

PI 1196791

REC'D 26 JUL 2004

WIPO

PCT

# THE UNITED STATES OF AMERICA

**TO ALL TO WHOM THESE PRESENTS SHALL COME:**

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office

July 22, 2004

**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.**

**APPLICATION NUMBER: 60/462,795**

**FILING DATE: April 14, 2003**

**RELATED PCT APPLICATION NUMBER: PCT/US04/11253**

By Authority of the  
COMMISSIONER OF PATENTS AND TRADEMARKS



M. SIAS  
Certifying Officer

**PRIORITY DOCUMENT**  
SUBMITTED OR TRANSMITTED IN  
COMPLIANCE WITH  
RULE 17.1(a) OR (b)

**PROVISIONAL APPLICATION FOR PATENT COVER SHEET**

This is a request for filing a **PROVISIONAL APPLICATION FOR PATENT** under 37 CFR 1.53 (c).

DOCKET NUMBER

21388PV

**INVENTOR(S)**

Given Name (first and middle (if any))	Family Name or Surname	Residence (City and either State or Foreign Country)
RAYMOND JOHN Y. JOSEPH S. LISA	CVETOVICH CHUNG AMATO DiMICHELE	SCOTCH PLAINS, NJ EDISON, NJ MILLERTON, NY BERKELEY HEIGHTS, NJ

☐ Additional inventors are being named on the separately numbered sheets attached hereto

**TITLE OF THE INVENTION (500 characters max)**

PROCESS AND INTERMEDIATES FOR THE PREPARATION OF PYRROLIDINE CARBOXYLIC ACIDS

**CORRESPONDENCE ADDRESS**

Direct all Correspondence to:

Merck & Co., Inc.  
Patent Department - RY60-30  
P.O. Box 2000  
Rahway

☒ Customer Number

000210

STATE

New Jersey

ZIP CODE

07065

COUNTRY

U.S.A.

**ENCLOSED APPLICATION PARTS (check all that apply)**

☒ Specification *Number of Pages* 55  
☐ Drawing(s) *Number of Sheets*  
☐ Application Data Sheet. See 37 CFR 1.76

☐ CD(s), Number

☐ Other (specify)

**METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)**

☐ A check or money order is enclosed to cover the filing fees

☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number:

13-2755

FILING FEE  
AMOUNT (\$)

\$160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE

*Barbel R. Brown*

Date 04/14/2003

TYPED or PRINTED NAME BAERBEL R. BROWN

REGISTRATION NO.  
(if appropriate)

47,449

TELEPHONE (732)594-0672

**EXPRESS MAIL CERTIFICATE**

DATE OF DEPOSIT April 14, 2003

EXPRESS MAIL NO. EV162774034US

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL "POST OFFICE TO ADDRESSEE" ON THE ABOVE DATE IN AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231.

MAILED BY

*Don Schepis*

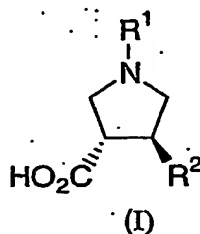
DATE April 14, 2003

In Duplicate

**TITLE OF THE INVENTION**  
**PROCESS AND INTERMEDIATES FOR THE PREPARATION OF**  
**PYRROLIDINE CARBOXYLIC ACIDS**

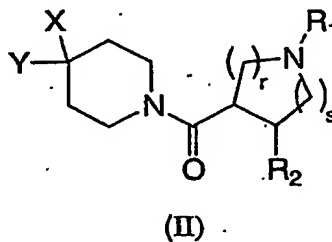
**5 BACKGROUND OF THE INVENTION**

The present invention provides a process for the preparation of pyrrolidine carboxylic acids of general formula (I).



The present invention also provides intermediates useful in the disclosed process.

The compounds of formula (I) are intermediates useful for the preparation of the pyrrolidine compounds of the general formula (II), wherein R<sub>2</sub> is phenyl, unsubstituted or substituted with one to three R<sub>3</sub> groups, r is 1 and s is 1.



15

The compounds of formula (II), along with their use as melanocortin receptor agonists were disclosed in WO 02/068387 (published on September 6, 2002), and WO 02/068388 (published on September 6, 2002). The compounds of formula (II) are also useful as agents for the treatment, control or prevention of diseases, disorders or conditions responsive to the activation of one or more of the melanocortin receptors including, but are not limited to, MC-1, MC-2, MC-3, MC-4, or MC-5. Such diseases, disorders or conditions include, but are not limited to, obesity, diabetes mellitus, hypertension, hyperlipidemia, osteoarthritis, cancer, gall

20

bladder disease, sleep apnea, depression, anxiety, compulsion, neuroses, insomnia/sleep disorder, substance abuse, pain, male and female sexual dysfunction, fever, inflammation, immune modulation, rheumatoid arthritis, skin tanning, acne and other skin disorders, neuroprotective and cognitive and memory enhancement

5 including the treatment of Alzheimer's disease. Some compounds encompassed by formula (II) show highly selective affinity for the melanocortin-4 receptor (MC-4R) relative to MC-1R, MC-2R, MC-3R, and MC-5R, which makes them especially useful in the prevention and treatment of obesity, as well as male and/or female sexual dysfunction, including erectile dysfunction.

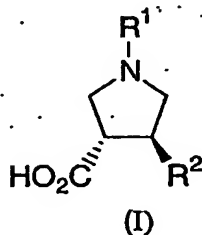
10 WO 02/068387 and WO 02/068388 describe processes for preparing the compounds of formula (II). However, the pyrrolidine acid was prepared in racemic forms and required a chiral HPLC chromatography. This resulted in the loss of all of the material prepared as the wrong enantiomer.

The present invention is directed to an efficient chiral synthesis that  
15 produces a pyrrolidine acid of structural formula (I) in a higher yield and utilizes less expensive chemical reagents. The synthetic sequence comprises 5 steps with an overall yield of about 71% and a chiral purity of >99.9 % ee of the pyrrolidine acid without the use of chromatography.

The synthesis of phenyl- and benzyl-substituted racemic pyrrolidines  
20 by intramolecular C-alkylation is described in Achini, R., *Helvetica Chimica Acta*, 64, 2203-2218 (1981). The asymmetric reduction of aryl chloromethyl-ketones is described in using (S)-MeCBS is described in Burkhardt, E.R. *Tetr. Lett.* 38, 1523-1526 (1997). The asymmetric transfer hydrogenation of ring-substituted 2-chloroacetophenone is reported by Noyori, et al., *Org. Lett.* 4, 4373 (2002). The  
25 reduction of 2-chloro-2',4'-difluoroacetophenone with NaBH<sub>4</sub>/Me<sub>3</sub>SiCl catalyzed by (S)- $\alpha,\alpha$ -diphenylpyrrolidinemethanol to give chlorohydrins is described in Jiang et al., *Tetr. Lett.*, 41, 10281-10283 (2000). The rate acceleration of the Michael addition of tertiary amines to acrylonitrile using a polar solvent is disclosed in Aggarwal, V. et al., *J. Org. Chem.* 67, 510-514 (2002).

## 30 SUMMARY OF THE INVENTION

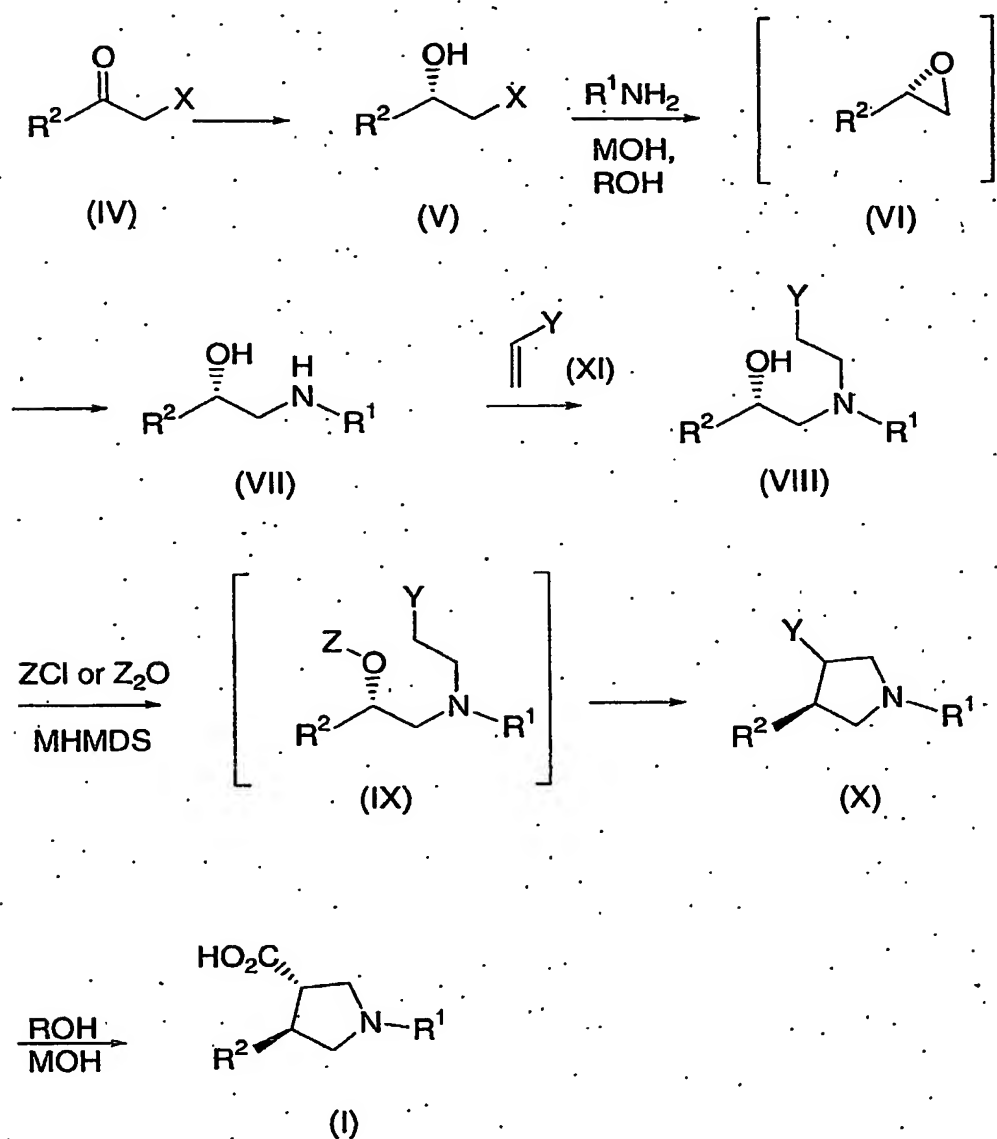
This invention is concerned with a process for preparing compounds of structural formula (I) and certain useful intermediates obtained during that process.



The novel process and novel intermediates can be exemplified in Scheme A, which shows the preparation of pyrrolidine acid (I).

- The process involves the chiral reduction of the halogenated ketone (IV) to form a halogenated alcohol (V). The halogenated alcohol (V) is then converted to the amino alcohol (VII), via the epoxide intermediate (VI), by treatment with a base and subsequent treatment with a primary amine. The conjugate addition of the resulting amino alcohol (VII) to an  $\alpha,\beta$  unsaturated nitrile or ester ( $Y = -CN$  or  $-CO_2R^5$ , and  $R^5$  is  $C_{1-4}$  alkyl) affords the tertiary amine (VIII). The alcohol of compound (VIII) is then converted to a leaving group (shown as -OZ in intermediate IX) by treatment with an alcohol activating reagent, such as  $ClPO(OR^6)_2$ ,  $ClPO(N(R^6)_2)_2$ ,  $MsCl$ ,  $Ms_2O$ ,  $TsCl$  or  $Ts_2O$ . The resulting intermediate (IX) is then treated with a base to facilitate the intramolecular cyclization to give a cis/trans mixture of pyrrolidine (X). The Y group of pyrrolidine (X) is then hydrolyzed /epimerized give the trans pyrrolidine acid (I).

## Scheme A

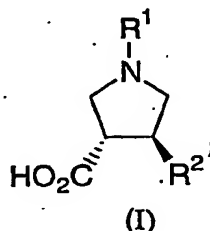


X is Br or Cl; Y is -CN or  $-CO_2R^5$ ;  $R^5$  is  $C_{1-4}$  alkyl; M is an alkaline metal, such as Li, Na, or K; Z is  $-PO(OR^6)_2$ ,  $-PO(N(R^6)_2)_2$ , Ms, or Ts;  $R^6$  is  $C_{1-4}$  alkyl or phenyl; R is H or  $C_{1-4}$  alkyl; and  $R^1$  and  $R^2$  are as defined supra.

Also provided are intermediate compounds which are useful for the preparation of compounds of structural formula (I).

# DETAILED DESCRIPTION OF THE INVENTION

- 5           The present invention provides a process for the preparation of compounds of structural formula (I):



wherein

- 10    R<sup>1</sup> is selected from the group consisting of

- (1) hydrogen,
- (2) amidino,
- (3) C<sub>1-4</sub> alkyliminoyl,
- (4) C<sub>1-10</sub> alkyl,
- 15   (5) -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-7</sub> cycloalkyl,
- (6) -(CH<sub>2</sub>)<sub>n</sub>-phenyl,
- (7) -(CH<sub>2</sub>)<sub>n</sub>-naphthyl, and
- (8) -(CH<sub>2</sub>)<sub>n</sub>-heteroaryl,

- 20    in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R<sup>3</sup>; and alkyl, cycloalkyl, and (CH<sub>2</sub>)<sub>n</sub> are unsubstituted or substituted with one to three groups independently selected from R<sup>3</sup> and oxo;

R<sup>2</sup> is selected from the group consisting of

- 25   (1) C<sub>1-4</sub> alkyl,
- (2) -(CH<sub>2</sub>)<sub>n</sub>-cycloalkyl,
- (3) -(CH<sub>2</sub>)<sub>n</sub>-heterocycloalkyl,
- (4) -(CH<sub>2</sub>)<sub>n</sub>-phenyl,
- (5) -(CH<sub>2</sub>)<sub>n</sub>-naphthyl, and

(6)  $-(CH_2)_n$ -heteroaryl wherein heteroaryl is selected from the group consisting of

- (1) pyridinyl,
- (2) furyl,
- 5 (3) thienyl,
- (4) pyrrolyl,
- (5) oxazolyl,
- (6) thiazolyl,
- (7) imidazolyl,
- 10 (8) pyrazolyl,
- (9) isoxazolyl,
- (10) isothiazolyl,
- (11) pyrimidinyl,
- (12) pyrazinyl,
- 15 (13) pyridazinyl,
- (14) quinolyl,
- (15) isoquinolyl,
- (16) benzimidazolyl,
- (17) benzofuryl,
- 20 (18) benzothieryl,
- (19) indolyl,
- (20) benzthiazolyl, and
- (21) benzoxazolyl;

in which alkyl, phenyl, naphthyl, heteroaryl, and  $(CH_2)_n$  are unsubstituted or  
25 substituted with one to three groups independently selected from  $R^3$ ;

each  $R^3$  is independently selected from the group consisting of

- (1) C<sub>1-6</sub> alkyl,
- (2)  $-(CH_2)_n$ -phenyl,
- 30 (3)  $-(CH_2)_n$ -naphthyl,
- (4)  $-(CH_2)_n$ -heteroaryl,
- (5)  $-(CH_2)_n$ -heterocycloalkyl,
- (6)  $-(CH_2)_n$ C<sub>3-7</sub> cycloalkyl,
- (7) halogen,



- 21
- (8)  $OR^4$ ,  
 (9)  $-(CH_2)_nN(R^4)_2$ ,  
 (10)  $NO_2$ ,  
 (11)  $-(CH_2)_nNR^4SO_2R^4$ ,  
 5 (12)  $-(CH_2)_nSO_2N(R^4)_2$ ,  
 (13)  $-(CH_2)_nS(O)_pR^4$ ,  
 (14)  $CF_3$ ,  
 (15)  $CH_2CF_3$ ,  
 (16)  $OCF_3$ , and  
 10 (17)  $OCH_2CF_3$ ;

in which heteroaryl is as defined above; alkyl, phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C<sub>1-4</sub> alkyl, trifluoromethyl, and C<sub>1-4</sub> alkoxy; and wherein any methylene (CH<sub>2</sub>) carbon atom in  
 15 R<sup>3</sup> is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C<sub>1-4</sub> alkyl; or two substituents when on the same methylene (CH<sub>2</sub>) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

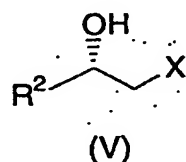
20 each R<sup>4</sup> is independently selected from the group consisting of

- (1) hydrogen,  
 (2) C<sub>1-6</sub> alkyl,  
 (3)  $-(CH_2)_n$ -phenyl,  
 (4)  $-(CH_2)_n$ -heteroaryl,  
 25 (5)  $-(CH_2)_n$ -naphthyl,  
 (6)  $-(CH_2)_n$ -heterocycloalkyl,  
 (7)  $-(CH_2)_nC_{3-7}$  cycloalkyl, and  
 (8)  $-(CH_2)_nC_{3-7}$  bicycloalkyl;

wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, and cycloalkyl are unsubstituted  
 30 or substituted with one to three groups independently selected from halogen, C<sub>1-4</sub> alkyl, hydroxy, and C<sub>1-4</sub> alkoxy; or two R<sup>4</sup> groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC<sub>1-4</sub> alkyl; and  
 n is 0, 1, 2, 3 or 4;

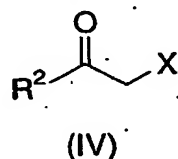
comprising the steps of:

- (a) preparing an alcohol of structural formula (V)



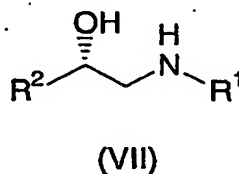
5 wherein

X is bromide or chloride, and R<sup>2</sup> is as defined above,  
by treating a ketone of structural formula (IV),



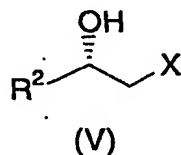
- 10 wherein X is bromide or chloride, and R<sup>2</sup> is as defined above, with a reducing agent,  
and isolating the resulting product;

- (b) forming an amino alcohol of structural formula (VII)



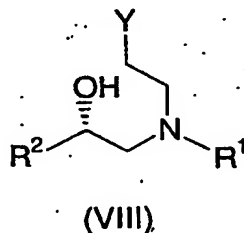
wherein R<sup>1</sup> and R<sup>2</sup> are as defined above,

- 15 by treating an alcohol of structural formula (V), wherein X is chloride or bromide and  
R<sup>2</sup> is as defined above,



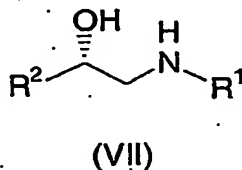
with an amine of general formula  $R^1NH_2$ , wherein  $R^1$  is as defined above, and a base in a solvent, and isolating the resulting product;

(c) forming a compound of structural formula (VIII)



wherein Y is  $-CN$  or  $-CO_2R^5$  and  $R^5$  is  $C_{1-4}$  alkyl, and wherein  $R^1$  and  $R^2$  are as defined above,

by treating the amino alcohol of structural formula (VII)

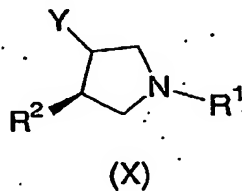


10 with a compound of general formula (XI)



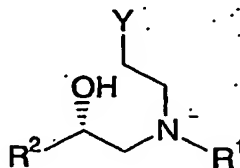
wherein Y is  $-CN$  or  $-CO_2R^5$ , and  $R^5$  is  $C_{1-4}$  alkyl, and isolating the resulting product;

15 (d) forming a pyrrolidine compound of structural formula (X)



21

wherein  $R^1$  and  $R^2$  are as defined above,  
 by treating the compound of structural formula (VIII), wherein Y,  $R^1$  and  $R^2$  are as defined above,

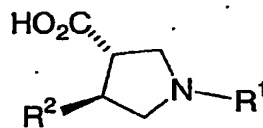


(VIII)

5

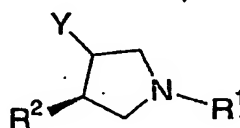
with an alcohol activating reagent, followed by a base;

(e) forming a trans-pyrrolidine acid of structural formula (I)



(I)

10 wherein  $R^1$  and  $R^2$  are as defined above,  
 by hydrolyzing the pyrrolidine compound of structural formula (X), wherein Y,  $R^1$  and  $R^2$  are as defined above,



(X)

15

with an aqueous base in a solvent; and

(f) isolating the resulting product.

In one embodiment of the present invention,  $R^2$  is phenyl or thienyl optionally substituted with one to three groups independently selected from  $R^3$ . In a

class of this embodiment,  $R^2$  is phenyl optionally substituted with one to three groups independently selected from  $R^3$ . In a subclass of this class,  $R^2$  is selected from the group of phenyl; *ortho*, *para*-difluorophenyl; and *para*-methoxyphenyl. In a subclass of this subclass,  $R^2$  is *ortho*, *para*-difluorophenyl.

5 In another embodiment,  $R^3$  is selected from the group consisting of halogen,  $-CF_3$ , and  $OR^4$ . In a class of this embodiment of the present invention,  $R^3$  is selected from the group consisting of fluoride, bromide, chloride,  $-CF_3$ , and  $-OC_{1-6}$  alkyl. In a subclass of this class,  $R^3$  is selected from fluoride, bromide,  $-CF_3$ , and  $-OCH_3$ .

10 In another embodiment,  $n$  is 0, 1 or 2. In a class of this embodiment  $n$  is 0 or 1. In a subclass of this embodiment,  $n$  is 0.

In another embodiment of the present invention, the reducing agent used to treat the compound of formula (IV) of step (a) is (+)-DIP chloride.

15 In another embodiment of the present invention, the compound of formula (IV) of step (a) is treated with a reducing agent in the presence of a catalyst. In a class of this embodiment the reducing agent is selected from the group consisting of borane-*N,N*-diethyl aniline, borane-THF, and borane-dimethylsulfide. In a subclass of this class, the reducing agent is borane-*N,N*-diethyl aniline. In another class of this embodiment, the catalyst is selected from the group consisting of (S)-  
20 CBS and (S)-2-methyl CBS oxazaborolidine. In a subclass of this class, the catalyst is (S)-2-methyl CBS oxazaborolidine.

In another embodiment of the present invention, alcohol of formula (V) is treated with an amine of general formula  $R^1NH_2$ , wherein  $R^1$  is selected from the group consisting of hydrogen,  $-(CH_2)_n$ phenyl, or  $C_{1-6}$ alkyl. In a class of this  
25 embodiment,  $R^1$  is *tert*-butyl or  $-CH_2$ -phenyl. In a subclass of this class,  $R^1$  is *tert*-butyl.

In another embodiment of the present invention, the alcohol of formula (V) is treated with a base selected from the group consisting of NaOH, LiOH, KOH. In a class of this embodiment, the base is NaOH.

30 In another embodiment of the present invention, the alcohol of formula (V) is treated in a solvent selected from methanol or ethanol. In a class of this embodiment, the solvent is methanol. In a subclass of this class, the solvent is refluxing methanol.

21

In another embodiment of the present invention, the amino alcohol of structural formula (VII) is isolated by recrystallization from heptane or hexane. In a class of this embodiment, the solvent is heptane.

In another embodiment of the present invention, the compound of  
5 formula (XI) is the compound wherein Y is CN.

In another embodiment of the present invention, the compound of formula (XI) is the compound wherein Y is  $-\text{CO}_2\text{R}^5$ , wherein  $\text{R}^5$  is  $\text{C}_{1-4}$  alkyl. In a class of this embodiment Y is  $-\text{CO}_2\text{CH}_3$ ,  $-\text{CO}_2\text{CH}_2\text{CH}_3$ , or  $-\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ . In a subclass of this class, Y is  $-\text{CO}_2\text{CH}_2\text{CH}_3$ , or  
10  $-\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ .

In another embodiment of the present invention, the compound of formula (VIII) is formed by heating the mixture to reflux.

In another embodiment of the present invention, the compound of formula (VIII) is formed by adding ethanol, formamide or a mixture thereof. In a  
15 class of this embodiment, the compound of formula (VIII) is formed by adding a 1:1 mixture of ethanol:formamide.

In another embodiment of the present invention, the compound of formula (VIII) is isolated by recrystallizing from heptane or hexane.

In another embodiment of the present invention, the compound of  
20 formula (VIII) is treated with an alcohol activating reagent selected from the group consisting of  $\text{ClPO}(\text{OR}^6)_2$ ,  $\text{ClPO}(\text{N}(\text{R}^6)_2)_2$ ,  $\text{MsCl}$ ,  $\text{Ms}_2\text{O}$ ,  $\text{TsCl}$ , and  $\text{Ts}_2\text{O}$ , wherein  $\text{R}^6$  is  $\text{C}_{1-4}$  alkyl or phenyl. In a class of this embodiment, the alcohol activating reagent is chlorodiethyl phosphate.

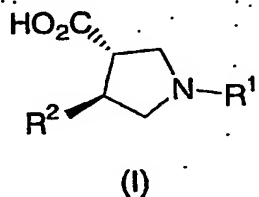
In another embodiment of the present invention, the compound of  
25 formula (VIII) is treated with a base selected from the group consisting of lithium hexamethyldisilazide, sodium hexamethyl disilazide, and potassium hexamethyldisilazide. In a class of this embodiment, the base is lithium hexamethyl disilazide.

In another embodiment of the present invention, the compound of  
30 formula (VIII) is treated at a temperature of about  $-30$  to about  $+10$  C. In a class of this embodiment, the temperature is about  $-15$  C.

In another embodiment of the present invention, the pyrrolidine compound of formula (X) is hydrolyzed with a base selected from the group consisting of  $\text{NaOH}$ ,  $\text{LiOH}$  and  $\text{KOH}$ . In one class of this embodiment, the base is  
35  $\text{NaOH}$ . In a subclass of this class, the base is aqueous  $\text{NaOH}$ .

In another embodiment of the present invention, the pyrrolidine compound of formula (X) is hydrolyzed in a solvent selected from the group consisting of methanol, ethanol, and isopropanol. In a class of this embodiment, the solvent is ethanol.

In another embodiment, the product of step (f) is isolated by forming a zwitterion of the trans pyrrolidine acid of structural formula (I)

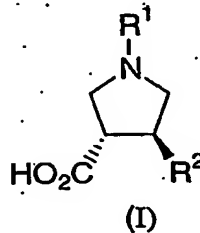


wherein R<sup>1</sup> and R<sup>2</sup> are as defined above, recrystallizing the zwitterion from a solvent; and isolating the resulting product.

In a class of this embodiment the zwitterion of the pyrrolidine acid of formula (I) is formed at the isoelectric pH using an acid. In one subclass of this class, the acid is selected from sulfuric acid or hydrochloric acid. In a subclass of this subclass, the acid is sulfuric acid. In another subclass of this class, the isoelectric pH is about 6 and a stoichiometric amount of acid is added.

In another class of this embodiment, the zwitterion of the pyrrolidine acid of formula (I) is recrystallized from a solvent selected from the group consisting of ethanol, isopropyl alcohol, methyl *tert*-butyl ether or a mixture thereof. In a subclass of this class, the solvent is a mixture of isopropyl alcohol and methyl *tert*-butyl ether. In a subclass of this subclass, the solvent is 1:3 isopropyl alcohol:methyl *tert*-butyl ether.

The present invention also provides a process for the preparation of compounds of structural formula (I):



wherein

R<sup>1</sup> is selected from the group consisting of

- (1) hydrogen,
- 5 (2) amidino,
- (3) C<sub>1-4</sub> alkyliminoyl,
- (4) C<sub>1-10</sub> alkyl,
- (5) -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-7</sub> cycloalkyl,
- (6) -(CH<sub>2</sub>)<sub>n</sub>-phenyl,
- 10 (7) -(CH<sub>2</sub>)<sub>n</sub>-naphthyl, and
- (8) -(CH<sub>2</sub>)<sub>n</sub>-heteroaryl,

in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R<sup>3</sup>; and alkyl, cycloalkyl, and (CH<sub>2</sub>)<sub>n</sub> are unsubstituted or substituted with one to three groups independently selected from R<sup>3</sup> and oxo;

R<sup>2</sup> is selected from the group consisting of

- (1) C<sub>1-4</sub> alkyl,
- (2) -(CH<sub>2</sub>)<sub>n</sub>-cycloalkyl,
- 20 (3) -(CH<sub>2</sub>)<sub>n</sub>-heterocycloalkyl,
- (4) -(CH<sub>2</sub>)<sub>n</sub>-phenyl,
- (5) -(CH<sub>2</sub>)<sub>n</sub>-naphthyl, and
- (6) -(CH<sub>2</sub>)<sub>n</sub>-heteroaryl wherein heteroaryl is selected from the group consisting of
- 25 (1) pyridinyl,
- (2) furyl,
- (3) thienyl,
- (4) pyrrolyl,
- (5) oxazolyl,
- 30 (6) thiazolyl,
- (7) imidazolyl,
- (8) pyrazolyl,
- (9) isoxazolyl,
- (10) isothiazolyl,
- 35 (11) pyrimidinyl,



- 5 (12) pyrazinyl,  
 (13) pyridazinyl,  
 (14) quinolyl,  
 (15) isoquinolyl,  
 (16) benzimidazolyl,  
 (17) benzofuryl,  
 (18) benzothienyl,  
 (19) indolyl,  
 (20) benzthiazolyl, and  
 10 (21) benzoxazolyl;

in which alkyl, phenyl, naphthyl, heteroaryl, and  $(CH_2)_n$  are unsubstituted or substituted with one to three groups independently selected from  $R^3$ ;

each  $R^3$  is independently selected from the group consisting of

- 15 (1)  $C_{1-6}$  alkyl,  
 (2)  $-(CH_2)_n$ -phenyl,  
 (3)  $-(CH_2)_n$ -naphthyl,  
 (4)  $-(CH_2)_n$ -heteroaryl,  
 (5)  $-(CH_2)_n$ -heterocycloalkyl,  
 20 (6)  $-(CH_2)_n C_{3-7}$  cycloalkyl,  
 (7) halogen,  
 (8)  $OR^4$ ,  
 (9)  $-(CH_2)_n N(R^4)_2$ ,  
 (10)  $NO_2$ ,  
 25 (11)  $-(CH_2)_n NR^4 SO_2 R^4$ ,  
 (12)  $-(CH_2)_n SO_2 N(R^4)_2$ ,  
 (13)  $-(CH_2)_n S(O)_p R^4$ ,  
 (14)  $CF_3$ ,  
 (15)  $CH_2 CF_3$ ,  
 30 (16)  $OCF_3$ , and  
 (17)  $OCH_2 CF_3$ ;

in which heteroaryl is as defined above; alkyl, phenyl, naphthyl, heteroaryl,  
 cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three  
 substituents independently selected from halogen, hydroxy, oxo,  $C_{1-4}$  alkyl,  
 35 trifluoromethyl, and  $C_{1-4}$  alkoxy; and wherein any methylene  $(CH_2)$  carbon atom in

$R^3$  is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C<sub>1-4</sub> alkyl; or two substituents when on the same methylene (CH<sub>2</sub>) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each  $R^4$  is independently selected from the group consisting of

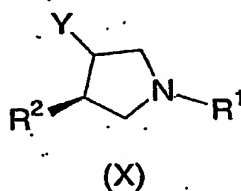
- (1) hydrogen,
- (2) C<sub>1-6</sub> alkyl,
- (3)  $-(CH_2)_n$ -phenyl,
- (4)  $-(CH_2)_n$ -heteroaryl,
- (5)  $-(CH_2)_n$ -naphthyl,
- (6)  $-(CH_2)_n$ -heterocycloalkyl,
- (7)  $-(CH_2)_n$ C<sub>3-7</sub> cycloalkyl, and
- (8)  $-(CH_2)_n$ C<sub>3-7</sub> bicycloalkyl;

wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from halogen, C<sub>1-4</sub> alkyl, hydroxy, and C<sub>1-4</sub> alkoxy; or two  $R^4$  groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC<sub>1-4</sub> alkyl; and

$n$  is 0, 1, 2, 3 or 4;

comprising the steps of:

- (a) hydrolyzing a pyrrolidine compound of structural formula (X), wherein Y,  $R^1$  and  $R^2$  are as defined above,



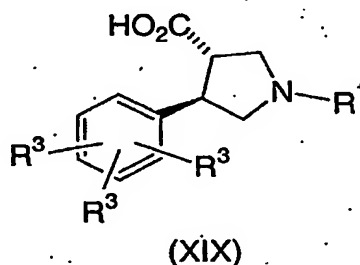
with an aqueous base in a solvent; and

- (b) isolating the resulting product.

In another embodiment of the present invention, the pyrrolidine compound of formula (X) is hydrolyzed with a base selected from the group consisting of NaOH, LiOH and KOH. In one class of this embodiment, the base is NaOH. In a subclass of this class, the base is aqueous NaOH.

5 In another embodiment of the present invention, the pyrrolidine compound of formula (X) is hydrolyzed in a solvent selected from the group consisting of methanol, ethanol, and isopropanol. In a class of this embodiment, the solvent is ethanol.

10 The present invention also provides a process for the preparation of compounds of structural formula (XIX):



wherein

R<sup>1</sup> is selected from the group consisting of

- 15 (1) hydrogen,
- (2) amidino,
- (3) C<sub>1-4</sub> alkyliminoyl,
- (4) C<sub>1-10</sub> alkyl,
- (5) -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-7</sub> cycloalkyl,
- 20 (6) -(CH<sub>2</sub>)<sub>n</sub>-phenyl,
- (7) -(CH<sub>2</sub>)<sub>n</sub>-naphthyl, and
- (8) -(CH<sub>2</sub>)<sub>n</sub>-heteroaryl,

in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R<sup>3</sup>; and alkyl, cycloalkyl, and (CH<sub>2</sub>)<sub>n</sub> are  
 25 unsubstituted or substituted with one to three groups independently selected from R<sup>3</sup> and oxo;

each R<sup>3</sup> is independently selected from the group consisting of

- 21
- 5
- 10
- 15
- (1) C<sub>1-6</sub> alkyl,
  - (2) -(CH<sub>2</sub>)<sub>n</sub>-phenyl,
  - (3) -(CH<sub>2</sub>)<sub>n</sub>-naphthyl,
  - (4) -(CH<sub>2</sub>)<sub>n</sub>-heteroaryl,
  - (5) -(CH<sub>2</sub>)<sub>n</sub>-heterocycloalkyl,
  - (6) -(CH<sub>2</sub>)<sub>n</sub>C<sub>3-7</sub> cycloalkyl,
  - (7) halogen,
  - (8) OR<sup>4</sup>,
  - (9) -(CH<sub>2</sub>)<sub>n</sub>N(R<sup>4</sup>)<sub>2</sub>,
  - (10) NO<sub>2</sub>,
  - (11) -(CH<sub>2</sub>)<sub>n</sub>NR<sup>4</sup>SO<sub>2</sub>R<sup>4</sup>,
  - (12) -(CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>N(R<sup>4</sup>)<sub>2</sub>,
  - (13) -(CH<sub>2</sub>)<sub>n</sub>S(O)<sub>p</sub>R<sup>4</sup>,
  - (14) CF<sub>3</sub>,
  - (15) CH<sub>2</sub>CF<sub>3</sub>,
  - (16) OCF<sub>3</sub>, and
  - (17) OCH<sub>2</sub>CF<sub>3</sub>;

in which heteroaryl is as defined above; alkyl, phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C<sub>1-4</sub> alkyl, trifluoromethyl, and C<sub>1-4</sub> alkoxy; and wherein any methylene (CH<sub>2</sub>) carbon atom in R<sup>3</sup> is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C<sub>1-4</sub> alkyl; or two substituents when on the same methylene (CH<sub>2</sub>) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R<sup>4</sup> is independently selected from the group consisting of

- 30
- (1) hydrogen,
  - (2) C<sub>1-6</sub> alkyl,
  - (3) -(CH<sub>2</sub>)<sub>n</sub>-phenyl,
  - (4) -(CH<sub>2</sub>)<sub>n</sub>-heteroaryl,
  - (5) -(CH<sub>2</sub>)<sub>n</sub>-naphthyl,
  - (6) -(CH<sub>2</sub>)<sub>n</sub>-heterocycloalkyl,
  - (7) -(CH<sub>2</sub>)<sub>n</sub>C<sub>3-7</sub> cycloalkyl, and

(8)  $-(CH_2)_n$  C<sub>3-7</sub> bicycloalkyl;

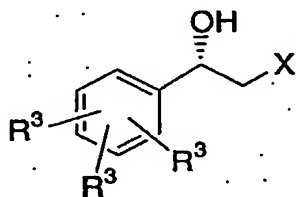
wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from halogen, C<sub>1-4</sub> alkyl, hydroxy, and C<sub>1-4</sub> alkoxy; or two R<sup>4</sup> groups together with the atom to which

5 they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC<sub>1-4</sub> alkyl; and

n is 0, 1, 2, 3, or 4;

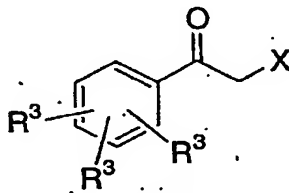
comprising the steps of:

10 (a) preparing an alcohol of structural formula (XIII)



(XIII)

wherein X is bromide or chloride, and R<sup>3</sup> is as defined above,  
by treating a ketone of structural formula (XII),



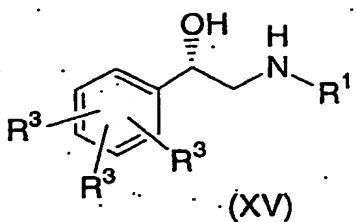
(XII)

15

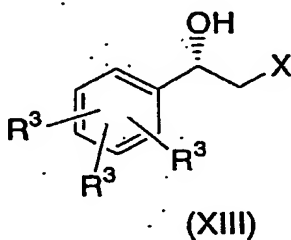
wherein X is bromide or chloride, and R<sup>3</sup> is as defined above, with a reducing agent, and isolating the resulting product;

(b) forming an amino alcohol of structural formula (XV)

20



wherein R<sup>1</sup> and R<sup>3</sup> are as defined above,  
by treating an alcohol of structural formula (XIII)

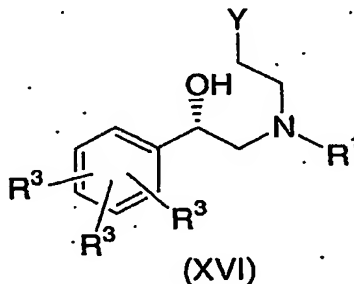


5

wherein X is chloride or bromide and R<sup>3</sup> are as defined above,  
with an amine of general formula R<sup>1</sup>NH<sub>2</sub>, wherein R<sup>1</sup> is as defined above,  
and a base in a solvent, and isolating the resulting product;

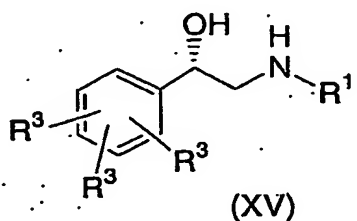
10

- (c) forming a compound of structural formula (XVI), wherein Y is -CN or -CO<sub>2</sub>R<sup>5</sup> and R<sup>5</sup> is C<sub>1-4</sub> alkyl, and R<sup>1</sup> and R<sup>3</sup> are as defined above,



15

by treating the amino alcohol of structural formula (XV) wherein R<sup>1</sup> and R<sup>3</sup> are as defined above,

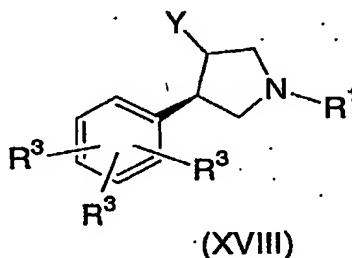


with a compound of general formula (XI)

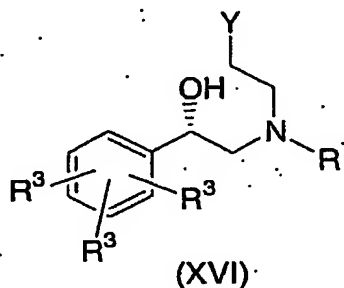


wherein Y is -CN or -CO₂R⁵, and R⁵ is C₁-₄ alkyl, and isolating the resulting product;

(d) forming a pyrrolidine compound of structural formula (XVIII) wherein Y, R¹ and R³ are as defined above,

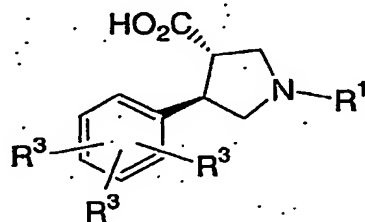


by treating the compound of structural formula (XVI), wherein Y, R¹ and R³ are as defined above,



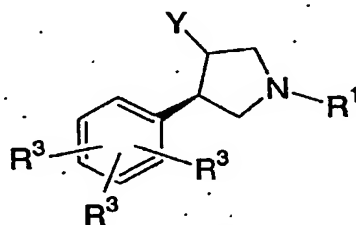
with an alcohol activating reagent, followed by a base;

- (e) forming a pyrrolidine acid of structural formula (XIX), wherein  $R^1$  and  $R^3$  are as defined above,



(XIX)

by hydrolyzing the pyrrolidine compound of structural formula (XVIII), wherein Y,  $R^1$  and  $R^3$  are as defined above,



(XVIII)

with an aqueous base in a solvent; and

- (f) isolating the resulting product.

In one embodiment,  $R^3$  is selected from the group consisting of halogen,  $-CF_3$ , and  $OR^4$ . In a class of this embodiment of the present invention,  $R^3$  is selected from the group consisting of fluoride, bromide, chloride,  $-CF_3$ , and  $-OC_{1-6}$  alkyl. In a subclass of this class,  $R^3$  is selected from fluoride, bromide,  $CF_3$ , and  $-OCH_3$ .

In another embodiment of the present invention, the reducing agent used to treat the compound of formula (XII) of step (a) is (+)-DIP chloride.

In another embodiment of the present invention, the compound of formula (XII) of step (a) is treated with a reducing agent in the presence of a catalyst. In a class of this embodiment the reducing agent is selected from the group consisting



of borane-N,N-diethyl aniline, borane-THF, and borane-dimethylsulfide. In a subclass of this class, the reducing agent is borane-N,N-diethyl aniline. In another class of this embodiment, the catalyst is selected from the group consisting of (S)-CBS and (S)-2-methyl CBS oxazaborolidine. In a subclass of this class, the catalyst  
5 is (S)-2-methyl CBS oxazaborolidine.

In another embodiment of the present invention, alcohol of formula (XIII) is treated with an amine of general formula  $R^1NH_2$ , wherein  $R^1$  is selected from the group consisting of hydrogen,  $-(CH_2)_n$ phenyl, or  $C_{1-6}$ alkyl. In a class of this embodiment,  $R^1$  is *tert*-butyl or  $-CH_2$ -phenyl. In a subclass of this class,  $R^1$  is  
10 *tert*-butyl.

In another embodiment of the present invention, the alcohol of formula (XIII) is treated with a base selected from the group consisting of NaOH, LiOH, KOH. In a class of this embodiment, the base is NaOH.

In another embodiment of the present invention, the alcohol of formula (XIII) is treated in a solvent selected from methanol or ethanol. In a class of this embodiment, the solvent is methanol. In a subclass of this class, the solvent is refluxing methanol.  
15

In another embodiment of the present invention, the amino alcohol of structural formula (XV) is isolated by recrystallization from heptane or hexane. In a  
20 class of this embodiment, the solvent is heptane.

In another embodiment of the present invention, the compound of formula (XI) is the compound wherein Y is CN.

In another embodiment of the present invention, the compound of formula (XI) is the compound wherein Y is  $-CO_2R^5$ , wherein  $R^5$  is  $C_{1-4}$  alkyl. In a  
25 class of this embodiment Y is  $-CO_2CH_3$ ,  $-CO_2CH_2CH_3$ , or  $-CO_2CH_2CH_2CH_2CH_3$ . In a subclass of this class, Y is  $-CO_2CH_2CH_3$ , or  $-CO_2CH_2CH_2CH_2CH_3$ .

In another embodiment of the present invention, the compound of structural formula (XVI) is formed by heating the mixture to reflux.

In another embodiment of the present invention, the compound of structural formula (XVI) is formed by adding ethanol, formamide or a mixture thereof. In a class of this embodiment, the compound of structural formula (XVI) is formed by adding a 1:1 mixture of ethanol:formamide.  
30

In another embodiment of the present invention, the compound of structural formula (XVI) is isolated by recrystallizing from heptane or hexane.  
35

In another embodiment of the present invention, the compound of structural formula (XVI) is treated with an alcohol activating reagent selected from the group consisting of  $\text{ClPO}(\text{OR}^6)_2$ ,  $\text{ClPO}(\text{N}(\text{R}^6)_2)_2$ ,  $\text{MsCl}$ ,  $\text{Ms}_2\text{O}$ ,  $\text{TsCl}$ , and  $\text{Ts}_2\text{O}$ , wherein  $\text{R}^6$  is  $\text{C}_{1-4}$  alkyl or phenyl. In a class of this embodiment, the alcohol activating reagent is chlorodiethyl phosphate.

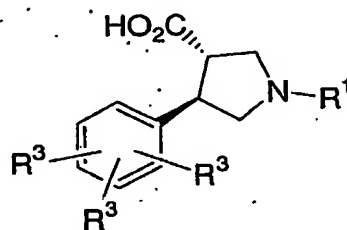
In another embodiment of the present invention, the compound of structural formula (XVI) is treated with a base selected from the group consisting of lithium hexamethyldisilazide, sodium hexamethyl disilazide, and potassium hexamethyldisilazide. In a class of this embodiment, the base is lithium hexamethyl disilazide.

In another embodiment of the present invention, the compound of structural formula (XVI) is treated at a temperature of about  $-30$  to about  $+10$  C. In a class of this embodiment, the temperature is about  $-15$  C.

In another embodiment of the present invention, the pyrrolidine compound of formula (XVIII) is hydrolyzed with a base selected from the group consisting of  $\text{NaOH}$ ,  $\text{LiOH}$  and  $\text{KOH}$ . In one class of this embodiment, the base is  $\text{NaOH}$ . In a subclass of this class, the base is aqueous  $\text{NaOH}$ .

In another embodiment of the present invention, the pyrrolidine compound of formula (XVIII) is hydrolyzed in a solvent selected from the group consisting of methanol, ethanol, and isopropanol. In a class of this embodiment, the solvent is ethanol.

In another embodiment, the product of step (f) is isolated by forming a zwitterion of the trans pyrrolidine acid of structural formula (XIX)



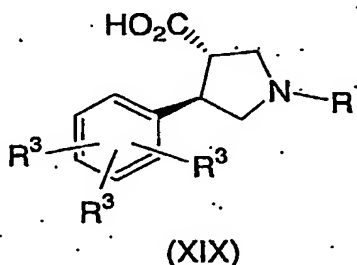
(XIX)

wherein  $\text{R}^1$  and  $\text{R}^3$  are as defined above; recrystallizing the zwitterion from a solvent; and isolating the resulting product.

In a class of this embodiment the zwitterion of the pyrrolidine acid of formula (XIX) is formed at the isoelectric pH using an acid. In one subclass of this class, the acid is selected from sulfuric acid or hydrochloric acid. In a subclass of this subclass, the acid is sulfuric acid. In another subclass of this class, the isoelectric pH is about 6 and a stoichiometric amount of acid is added.

In another class of this embodiment, the zwitterion of the pyrrolidine acid of formula (XIX) is recrystallized from a solvent selected from the group consisting of ethanol, isopropyl alcohol, methyl *tert*-butyl ether or a mixture thereof. In a subclass of this class, the solvent is a mixture of isopropyl alcohol and methyl *tert*-butyl ether. In a subclass of this subclass, the solvent is 1:3 isopropyl alcohol:methyl *tert*-butyl ether.

The present invention also provides a process for the preparation of compounds of structural formula (XIX):



wherein

R<sup>1</sup> is selected from the group consisting of

- (1) hydrogen,
- (2) amidino,
- (3) C<sub>1-4</sub> alkyliminoyl,
- (4) C<sub>1-10</sub> alkyl,
- (5) -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-7</sub> cycloalkyl,
- (6) -(CH<sub>2</sub>)<sub>n</sub>-phenyl,
- (7) -(CH<sub>2</sub>)<sub>n</sub>-naphthyl, and
- (8) -(CH<sub>2</sub>)<sub>n</sub>-heteroaryl,

in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from  $R^3$ ; and alkyl, cycloalkyl, and  $(CH_2)_n$  are unsubstituted or substituted with one to three groups independently selected from  $R^3$  and oxo;

each  $R^3$  is independently selected from the group consisting of

- (1)  $C_{1-6}$  alkyl,
- (2)  $-(CH_2)_n$ -phenyl,
- (3)  $-(CH_2)_n$ -naphthyl,
- (4)  $-(CH_2)_n$ -heteroaryl,
- (5)  $-(CH_2)_n$ -heterocycloalkyl,
- (6)  $-(CH_2)_n C_{3-7}$  cycloalkyl,
- (7) halogen,
- (8)  $OR^4$ ,
- (9)  $-(CH_2)_n N(R^4)_2$ ,
- (10)  $NO_2$ ,
- (11)  $-(CH_2)_n NR^4 SO_2 R^4$ ,
- (12)  $-(CH_2)_n SO_2 N(R^4)_2$ ,
- (13)  $-(CH_2)_n S(O)_p R^4$ ,
- (14)  $CF_3$ ,
- (15)  $CH_2 CF_3$ ,
- (16)  $OCF_3$ , and
- (17)  $OCH_2 CF_3$ ;

in which heteroaryl is as defined above; alkyl, phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo,  $C_{1-4}$  alkyl, trifluoromethyl, and  $C_{1-4}$  alkoxy; and wherein any methylene  $(CH_2)$  carbon atom in  $R^3$  is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and  $C_{1-4}$  alkyl; or two substituents when on the same methylene  $(CH_2)$  group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each  $R^4$  is independently selected from the group consisting of

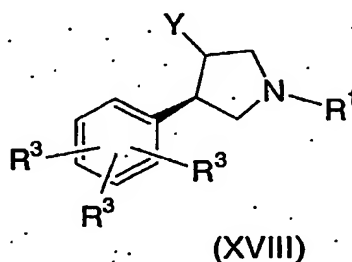
- (1) hydrogen,
- (2)  $C_{1-6}$  alkyl,

- (3)  $-(CH_2)_n$ -phenyl,  
 (4)  $-(CH_2)_n$ -heteroaryl,  
 (5)  $-(CH_2)_n$ -naphthyl,  
 (6)  $-(CH_2)_n$ -heterocycloalkyl,  
 5 (7)  $-(CH_2)_n$ C<sub>3-7</sub> cycloalkyl, and  
 (8)  $-(CH_2)_n$ C<sub>3-7</sub> bicycloalkyl;

wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from halogen, C<sub>1-4</sub> alkyl, hydroxy, and C<sub>1-4</sub> alkoxy; or two R<sup>4</sup> groups together with the atom to which  
 10 they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC<sub>1-4</sub> alkyl; and  
 n is 0, 1, 2, 3 or 4;

comprising the steps of:

- 15 (a) hydrolyzing a pyrrolidine compound of structural formula (XVIII), wherein Y, R<sup>1</sup> and R<sup>3</sup> are as defined above,



- 20 with an aqueous base in a solvent; and

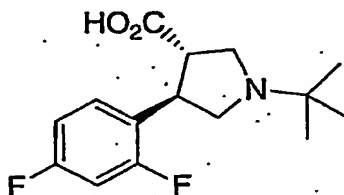
- (b) isolating the resulting product.

In another embodiment of the present invention, the pyrrolidine compound of formula (XVIII) is hydrolyzed with a base selected from the group consisting of NaOH, LiOH and KOH. In one class of this embodiment, the base is  
 25 NaOH. In a subclass of this class, the base is aqueous NaOH.

In another embodiment of the present invention, the pyrrolidine compound of formula (XVIII) is hydrolyzed in a solvent selected from the group consisting of

methanol, ethanol, and isopropanol. In a class of this embodiment, the solvent is ethanol.

In a further embodiment of this invention, the compound of formula I is compound 1-8



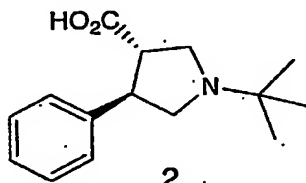
5

1-8

or a zwitterion or salt thereof. In a class of this embodiment, the zwitterion is formed by the addition of sulfuric acid or hydrochloric acid. In another class of this embodiment, the zwitterion is formed by the addition of sulfuric acid.

10

In a further embodiment of this invention, the compound of formula I is compound 2

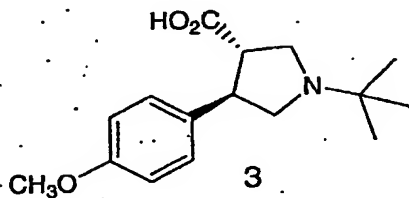


2

or a zwitterion or salt thereof. In a class of this embodiment, the zwitterion is formed by the addition of sulfuric acid or hydrochloric acid. In another class of this embodiment, the zwitterion is formed by the addition of sulfuric acid.

15

In a further embodiment of this invention, the compound of formula I is compound 3



or a zwitterion or salt thereof. In a class of this embodiment, the zwitterion is formed by the addition of sulfuric acid or hydrochloric acid. In another class of this embodiment, the zwitterion is formed by the addition of sulfuric acid.

5

Throughout the instant application, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration.

10 Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

The term "aryl" includes phenyl and naphthyl.

15

The term "heteroaryl" includes mono- and bicyclic aromatic rings containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur. "5- or 6-Membered heteroaryl" represents a monocyclic heteroaromatic ring. Examples of heteroaryls useful in this invention include wherein heteroaryl is selected from the group consisting of pyridinyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, benzimidazolyl, benzofuryl, benzothienyl, indolyl, benzthiazolyl, and benzoxazolyl, and the like. Bicyclic heteroaromatic rings include, but are not limited to, benzothiadiazole, indole, benzothiophene, benzofuran, benzimidazole, benzisoxazole, benzothiazole, quinoline, benzotriazole, benzoxazole, isoquinoline,

25

purine, furopyridine and thienopyridine. In one embodiment of the present invention, heteroaryl is selected from the group consisting of pyridinyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, triazolyl, triazinyl, tetrazolyl, thiadiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxathiazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, benzimidazolyl, benzofuryl, benzothienyl, indolyl, benzthiazolyl, and benzoxazolyl.

30

The term "cycloalkyl" is intended to include non-aromatic rings containing only carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

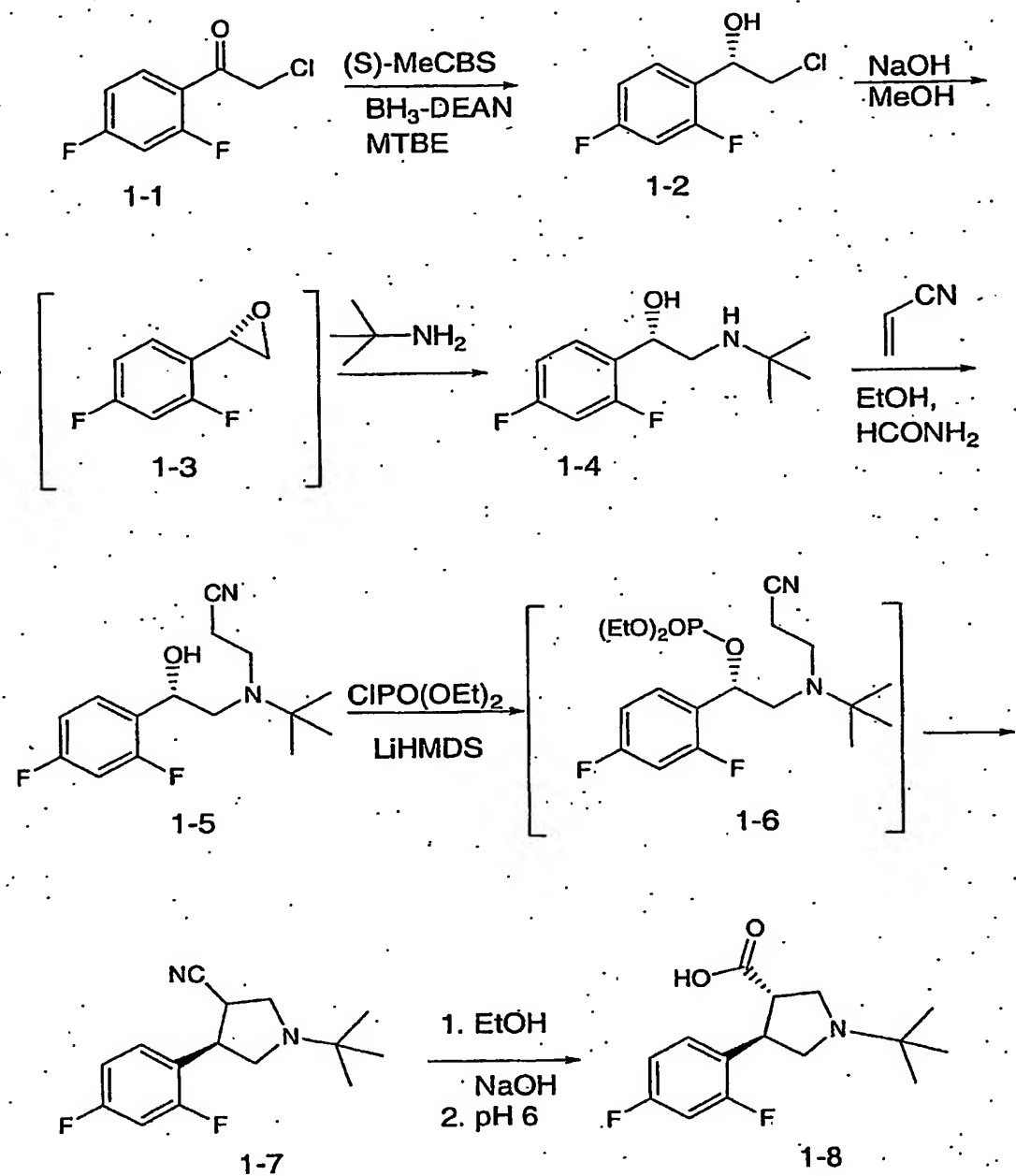
5 The term "heterocycloalkyl" is intended to include non-aromatic heterocycles containing one to four heteroatoms selected from nitrogen, oxygen and sulfur. Examples of a 5 or 6-membered heterocycloalkyl include piperidine, morpholine, thiamorpholine, pyrrolidine, imidazolidine, tetrahydrofuran, piperazine, and the like.

10 Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other; thus for example,  $\text{NR}^4\text{R}^4$  may represent  $\text{NH}_2$ ,  $\text{NHCH}_3$ ,  $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_3$ , and the like.

15 The process and intermediates of the present invention can be exemplified with the preparation of (3S,4R)-*N*-*tert*-Butyl-4(2,4-difluorophenyl)-pyrrolidine 3-carboxylic acid (1-8) as shown in Scheme 1.



Scheme 1



As shown in Scheme 1, the known (3S,4R)-*N*-*tert*-Butyl-4(2,4-difluorophenyl)pyrrolidine 3-carboxylic acid (1-8) is prepared as follows.

The asymmetric reduction of 2-chloro-2',4'-difluoroacetophenone 1-1 with a reducing agent, such as (+) DIP chloride; or with a reducing agent such as borane-diethyl aniline, borane dimethyl-sulfide, or borane-THF in the presence of a catalyst, such as (S)-CBS, or (S)-2-methyl CBS oxazaborolidine. The reaction is run in a solvent such as MTBE, toluene, or THF, at a temperature of about -20 to +60°C, and optimally at a temperature of about +30 to +50°C, to afford the (S)-alcohol 1-2. When (S)-2-methyl CBS oxazaborolidine and borane-diethyl aniline are used for the reduction, and the reduction is run at a temperature of about 40°C, then the use of 0.5 mole % of (S)-CBS catalyst results in the formation of 98.88 % ee of the *S*-enantiomer of alcohol 1-2. The *R*-enantiomer of alcohol 1-2 may be prepared by treating 1-1 with (-) DIP chloride, or by treating 1-1 with a borane reducing agent and a catalyst, such as (R)-CBS or (R)-2-methyl CBS oxazaborolidine under similar reaction conditions. By reducing 1-1 with the (-) DIP chloride, or with a borane reducing agent and (R)-CBS or (R)-2-methyl CBS oxazaborolidine, the 3*R*, 4*S* diastereomer of 1-1 may be made in a similar fashion. The reduction of acetophenone 1-1 may also be affected by treatment with sodium borohydride and trimethylsilyl chloride catalyzed by (S)- $\alpha,\alpha$ -diphenyl pyrrolidine methanol, or by treatment of acetophenone 1-1 via asymmetric transfer hydrogenation using chiral rhodium complex catalysis.

Treatment of alcohol 1-2 with a base, such as sodium hydroxide, lithium hydroxide or potassium hydroxide, in a protic solvent, such as methanol or ethanol, and subsequently heating to reflux results in the formation of the epoxide intermediate 1-3 *in situ*. Opening the epoxide ring with a primary amine, such as a C<sub>1-6</sub> alkyl amine, benzyl amine or substituted benzylamine, affords the amino alcohol 1-4. Crystallization of 1-4 from heptane or hexanes gives amino alcohol 1-4 as >99.9% ee of the *S*-enantiomer. When methanol and *tert*-butyl amine are used to prepare amino alcohol 1-4, the optimal ratio of methanol to *tert*-butyl amine is 1:5. The treatment of the epoxide intermediate 1-3 with benzyl amine and the subsequent removal of the benzyl protecting group under standard conditions, such as hydrogenation, is useful to prepare compounds of formula I in which R<sup>1</sup> is H.

Treatment of amino alcohol 1-4 with acrylonitrile and heating to reflux, followed by the addition of ethanol, formamide, or a mixture thereof, in the

21588PV

later stages of the reaction, affords the amino nitrile 1-5. The amino nitrile 1-5 may be further purified by recrystallizing from heptane or hexane.

The pyrrolidine nitrile 1-7 was formed by the conversion of the alcohol of nitrile 1-5 into a leaving group by treatment with an alcohol activating reagent, such as  $\text{ClPO}(\text{OEt})_2$ , to form intermediate 1-6 *in situ*. Subsequent treatment of intermediate 1-6 with a base, such as lithium hexamethyldisilazide, sodium hexamethyldisilazide or potassium hexamethyldisilazide, at a temperature of about  $-30$  to about  $+10^\circ\text{C}$  yields a cis/trans mixture of the pyrrolidine nitrile 1-7. Other alcohol activating reagents useful to convert the alcohol into a leaving group include, but are not limited to,  $\text{ClPO}(\text{OR}^6)_2$ ,  $\text{ClPO}(\text{N}(\text{R}^6)_2)_2$ ,  $\text{MsCl}$ ,  $\text{Ms}_2\text{O}$ ,  $\text{TsCl}$  or  $\text{Ts}_2\text{O}$ , wherein  $\text{R}^6$  is  $\text{C}_{1-4}$ alkyl or phenyl.

The kinetically controlled hydrolysis/epimerization of pyrrolidine nitrile 1-7 with an aqueous base, such as sodium hydroxide, lithium hydroxide or potassium hydroxide, in a protic solvent, such as methanol, ethanol, or isopropanol, at reflux, and the subsequent adjustment of the pH to the isoelectric point of 1-8 with an acid, such as sulfuric acid or  $\text{HCl}$ , affords the zwitterion 1-8. The pH at the isoelectric point is about pH 6. The zwitterion 1-8 may be recrystallized from ethanol to give the trans pyrrolidine acid zwitterion 1-8. Zwitterion 1-8 may also be recrystallized as an  $\text{HCl}$  salt from acetonitrile.

20

Abbreviations Used in the Description of the Preparation of the Compounds of the Present Invention: (S)-Me CBS and (S)-2-methyl-CBS-OAB are (S)-2-methyl CBS oxazaborolidine; BOC is tert-butyl carbamate; DEAN is diethyl aniline; DMF is *N,N*-dimethyl formamide; EtOAc is ethyl acetate; EtOH is ethanol; g is grams; h or hr is hours;  $\text{H}_2$  is hydrogen;  $\text{HCl}$  is hydrochloric acid, HPLC is high pressure liquid chromatography; mm Hg is millimeters of mercury; IPA is isopropyl alcohol; kg is kilograms; L is liters;  $\text{LiHMDS}$  is lithium hexamethyl disilazide; M is molar; mL is milliliters; MeOH is methanol, min is minutes, mol is moles; Ms is methanesulfonyl; MTBE is methyl t-butyl ether; N is normal; NMP is N-methyl pyrrolidinone; NaCl is sodium chloride; NMR is nuclear magnetic resonance; OAc is acetate; Ts is toluenesulfonyl; THF is tetrahydrofuran; and  $\text{ClPO}(\text{OEt})_2$  is chloro diethyl phosphate.

The following Example is provided to illustrate the invention and is not to be construed as limiting the scope of the invention in any manner. A

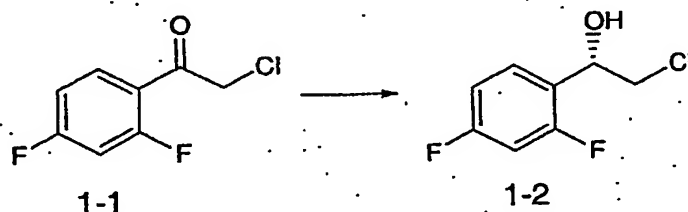
35

representative experimental procedure utilizing the novel process is detailed below. For purposes of illustration, the following Example is directed to the preparation of compound 1-8, but doing so is not intended to limit the present invention to a process for making that specific compound.

#### EXAMPLE 1

##### (3S,4R)-N-tert-Butyl-4(2,4-difluorophenyl)pyrrolidine 3-carboxylic acid (1-8)

##### Step A: Preparation of Compound 1-2



A solution of (S)-2-methyl-CBS-OAB (128 mL of 1.0M solution in toluene, Aldrich), borane-*N,N*-diethylaniline (25.7 mol, Callery) in MTBE (10 L) was heated to 38-42 °C, followed by the addition of a solution of 2-chloro-2',4'-di-fluoro-acetophenone (4891 g, Apollo) in MTBE (14.7 L) over 10 hours. The resulting homogeneous solution was stirred at 40 °C for one hour, and then cooled to 18 °C and stirred overnight. Methanol (2.3 L) was added over 60 minutes, while maintaining the temperature at <20 °C with cooling. The resulting homogeneous solution was stirred for 30 minutes, then dilute with water (24 L) and 5 N aqueous HCl (10 L) was added over 30 minutes, while maintaining the temperature at 22-25 °C with cooling. After stirring 30 minutes, the layers were separated. The organic layer was washed with saturated aqueous NaCl, and then concentrated *in vacuo* to give chloro-alcohol 1-2. The chiral assay of the chloro-alcohol gave a 99.44:0.56 ratio of S:R enantiomers (98.88% ee).

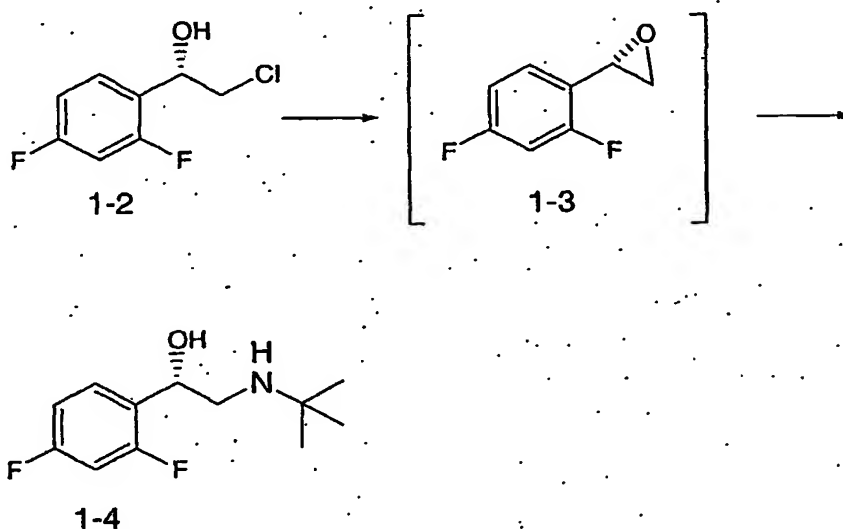
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400.25 MHz) δ 7.51 (m, 1H), 6.91 (m, 1H), 6.80 (m, 1H), 5.16 (dd, *J* = 8.2, 3.2 Hz, 1H), 3.79 (dd, *J* = 11.2, 3.4 Hz, 1H), 3.62 (dd, *J* = 11.2, 8.2 Hz, 1H), 3.02 (s, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.65 MHz)  $\delta$  162.7 (dd,  $J = 249.6$ , 12.0 Hz), 159.7 (dd,  $J = 248.5$ , 11.7 Hz), 128.6 (dd,  $J = 9.7$ , 5.7 Hz), 123.0 (dd,  $J = 13.5$ , 3.8 Hz), 111.6 (dd,  $J = 21.2$ , 3.7 Hz), 103.8 (t,  $J = 25.4$  Hz), 67.8 (d, 2.1 Hz), 49.4.

BP: 69-71 °C at 15 mm Hg.

5

Step B: Preparation of Compound 1-4



The concentrated MTBE solution of 1-2 from Step A (5040 g, 25.67 mol) was diluted with methanol (5 L), then *tert*-butylamine (25 L) was added. The mixture warmed upon mixing to 45 °C. The mixture was then cooled to 25 °C and solid NaOH pellets (1048 g) were added. No exotherm was observed, and the mixture was stirred and warmed to reflux. After 2 hours, if chloro-alcohol remains, additional NaOH can be added. After 12-20 hours of refluxing, the mixture was concentrated *in vacuo* to 1/3 volume, then water (5 L) and MTBE (20 L) were added. The resulting layers were separated, and the aqueous phase was re-extracted with MTBE (2 x 2 L). The combined extracts were washed with saturated aqueous NaCl (1 L), then concentrated *in vacuo*. Heptane (40 L) was added and the concentration was continued to bring the volume to 20 L. The resulting mixture was then heated to ~90 °C to dissolve all solids, and allowed to cool to 22 °C to crystallize over 4 hours. The mixture was then cooled to 0 °C, stirred 12-15 hr, and filtered. The filtrate was washed with cold heptane (2 x 5 L), then dried *in vacuo* at 35 °C to obtain the

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400.25 MHz) δ 7.52 (m, 1H), 6.88 (m, 1H), 6.76 (m, 1H), 4.85 (dd, *J* = 8.6, 3.4, 1H), 2.94 (m, 1H), 2.52 (m, 1H), 1.10 (s, 9H).

10

25

L volume and flushed with 5 x 6 L portions of *n*-heptane, during which time product crystallized. The slurry was diluted with *n*-heptane to a volume of 23 L. The mixture was stirred at 0-5 °C for 3 days, then filtered and washed with cold (5 °C) *n*-heptane (14 L). The wet cake was dried *in vacuo* at 20 °C with a nitrogen sweep for 4 days to afford nitrile 1-5 as a crystalline white solid. The chiral assay of crystalline nitrile 1-5 was >99.99 area % as the desired S-enantiomers.

<sup>1</sup>H-NMR (400.25 MHz, CDCl<sub>3</sub>) δ 7.55 (m, 1H), 6.90 (m, 1H), 6.77 (m, 1H), 4.84 (dd, *J* = 10.2, 3.1, 1H), 3.66 (OH, 1H), 3.00-2.83 (om, 3H), 2.62-2.47 (om, 2H), 2.45 (dd, *J* = 13.9, 10.3, 1H), 1.15 (s, 9H).

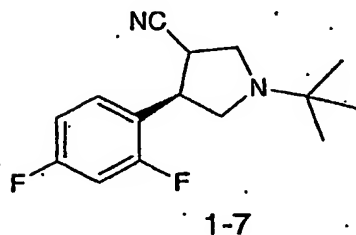
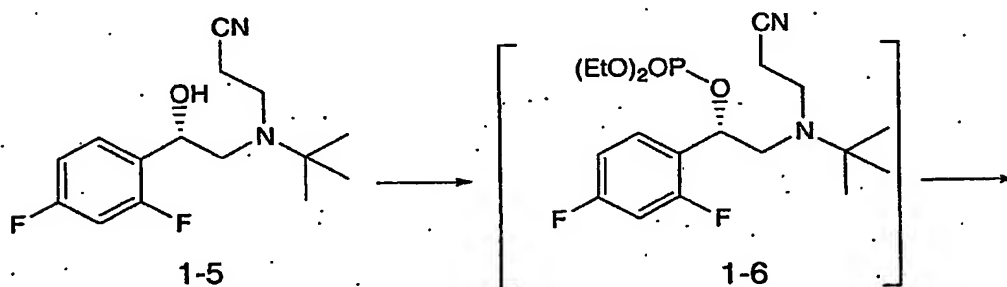
<sup>13</sup>C-NMR (100.65 MHz, CDCl<sub>3</sub>) δ 162.1 (dd, *J* = 247.7, 11.9), 159.6 (dd, *J* = 247.5, 11.9), 128.0 (dd, *J* = 9.5, 6.5), 125.1 (dd, 13.7, 3.6), 118.6, 111.4 (dd, *J* = 20.9, 3.3), 103.4 (t, *J* = 25.6), 65.4, 57.9, 55.7, 47.3, 27.2 (3C), 20.2.

<sup>19</sup>F-NMR (376.61 MHz, CDCl<sub>3</sub>) δ -112.25 (d, *J* = 6.9), -116.27 (d, 6.8).

MP (DSC): onset 60.20 °C, end 64.15 °C, peak 62.61 °C.

Anal. Calcd for C<sub>15</sub>H<sub>20</sub>F<sub>2</sub>N<sub>2</sub>O: Calc., C, 63.81, H, 7.14, N, 9.92, F, 13.46. Found, C, 63.79, H, 7.30, N, 9.93, F, 13.31.

#### Step D: Preparation of Compound 1-7



To a solution of alcohol 1-5 (5.73 kg, 99.9%, 20.28 mol) in dry THF (31.3 L), cooled to -20 °C, was added chloro diethylphosphate (3.79 kg, 21.29 mol). Lithium hexamethyldisilazide (1.35 M in THF; 31.5 L, 42.58 mol) was slowly added over 1.5 hours while maintaining the reaction temperature at  $-15 \pm 3$  °C. After stirring at -15 °C for 2 hours, the HPLC assay confirmed complete conversion to pyrrolidine 1-7 (as a 80:20 trans:cis mixture).

The reaction mixture was quenched with water (50.6 L) at <15 °C and extracted with n-heptane (40.5 L) at 20 °C. The organic layer was washed with 10% aqueous NaCl solution (52 L). The organic layer was carefully extracted with 3 N HCl solution (40.6 L, 121.8 mol) with cooling to keep the temperature <35 °C. The aqueous layer (58 L) was adjusted to pH 11-12 with 50% aq NaOH (6.13 L, 116.1 mol) and extracted with n-heptane (54 L). The layers were separated. The organic layer was washed once with 10% aqueous NaCl solution (26 L) and the resulting heptane solution (48 kg total) was assayed by HPLC to contain cyclized nitrile 1-7 (as a 80:20 trans:cis mixture), which was used, as is, in the hydrolysis/epimerization reaction in Step E.

#### Trans- Pyrrolidine Nitrile-HCl Salt

<sup>1</sup>H-NMR (400.25 MHz, D<sub>2</sub>O)  $\delta$  7.42 (m, 1H), 7.03-6.96 (om, 2H), 4.06-3.79 (om, 5H), 3.46 (bt,  $J = 11.6$ , 1H), 1.38 (s, 9H).  
<sup>13</sup>C-NMR (100.65 MHz, D<sub>2</sub>O)  $\delta$  163.2 (dd,  $J = 180.9$ , 12.6), 160.8 (dd,  $J = 180.8$ , 12.7), 130.2 (dd,  $J = 10.2$ , 5.4), 116.9, 116.8, 112.1 (dd,  $J = 21.7$ , 3.4), 104.6 (t,  $J = 26.0$ ), 63.2, 51.1, 49.3, 41.4, 32.3, 23.7 (3C).  
<sup>19</sup>F-NMR (376.61 MHz, D<sub>2</sub>O)  $\delta$  -109.87 (d,  $J = 7.7$ ), -112.87 (d,  $J = 8.5$ ).  
 MP (DSC): onset 179.23 °C, end 182.83 °C, peak 181.85 °C.  
 HR-MS M+H theoretical 265.1516; found 265.1517.

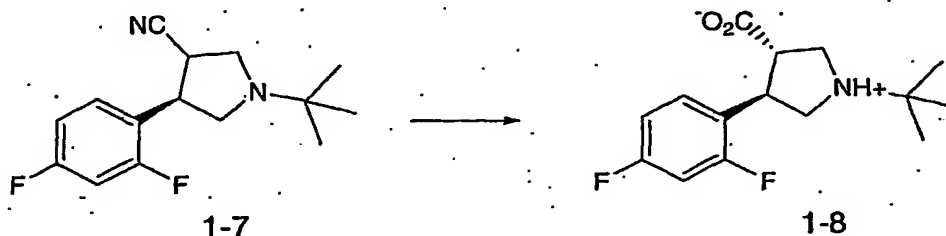
#### Cis- Pyrrolidine Nitrile-HCl Salt

<sup>1</sup>H-NMR (d<sub>4</sub>-CH<sub>3</sub>OH, 400.25 MHz)  $\delta$  7.57 (m, 1H), 7.16-7.03 (om, 2H), 4.82 (s, OH), 4.20-4.08 (m, 2H), 4.07-3.90 (m, 3H), 3.89-3.76 (m, 1H), 1.53 (s, 9H).  
<sup>13</sup>C-NMR (d<sub>4</sub>-CH<sub>3</sub>OH, 100.65 MHz)  $\delta$  165.0 (dd,  $J = 193.3$ , 12.5), 162.5 (dd,  $J = 192.9$ , 12.5), 131.5, 118.9 (dd,  $J = 14.3$ , 3.7), 118.3, 113.0 (dd,  $J = 21.7$ , 3.5), 105.4 (t,  $J = 26.2$ ), 64.2, 51.8, 51.1, 40.2, 35.0, 24.9 (3C).  
<sup>19</sup>F-NMR (376.61 MHz, d<sub>4</sub>-CH<sub>3</sub>OH)  $\delta$  -111.29, -112.61 (d,  $J = 6.8$ ).  
 MP (DSC): onset 257.91 °C, end 263.37 °C, peak 262.15 °C.



Anal. Calcd for  $C_{15}H_{19}ClF_2N_2$ : Calc., C, 59.90, H, 6.37, N, 9.31, F, 12.63, Cl, 11.79. Found, C, 59.76, H, 6.26, N, 9.40, F, 12.54, Cl, 11.43.

5 Step E: Preparation of Compound 1-8



A solution of crude pyrrolidine nitrile 1-7 (4.88 kg, 18.46 mol) in *n*-heptane (~65 L total) from Step D was solvent-switched to ethanol (~20.6 L total) by distilling the *n*-heptane (50-60 torr, 25 °C) down to about 6 L in volume, and adding ethanol (15 L). The resulting solution was concentrated to a 6 L volume, and diluted with ethanol (14.6 L) to give a total volume of 20.6 L. To this solution was added 50% aqueous NaOH (2.7 L, 51.15 mol) over 2 minutes with stirring. This mixture was then heated to reflux (78-80 °C) under nitrogen for 5 to 6 hours. The reaction was monitored by HPLC. After cooling to 20 °C, the reaction mixture was diluted with ethanol (25.4 L) and methanol (40.6 L) to give a total volume of ~88 L (as a 1:1 MeOH:EtOH mixture). This solution was cooled to 12 °C and 96%  $H_2SO_4$  (1.42 L, 25.6 mol) was added, while maintaining the temperature at about 20 °C. The slurry was filtered through a bed of Solka-Floc (5 kg) and anhydrous powder  $Na_2SO_4$  (4 kg), and then washed with 1:1 EtOH:MeOH (60 L). The resulting filtrate was re-filtered, concentrated and solvent-switched to a 2-propanol solution (~15 L volume) by vacuum-distillation. The product crystallized during solvent switching.

The resulting slurry was heated to reflux (~80 °C) for 2 hours (which only partly dissolves product). The mixture was then allowed to cool. After cooling to 16 °C, MTBE (30.4 L, 3 volumes relative to IPA) was added to the mixture over 5 hours to give a 1:3 ratio of IPA:MTBE. After stirring at 16-17 °C for 3 days, the slurry was filtered, and the solids were washed with 12 L 1:3 IPA:MTBE. The solids were dried *in vacuo* (150 torr) at 50 °C, with a nitrogen sweep through the batch, for 3 days.

Zwitterion 1-8 was isolated as a white crystalline solid. Zwitterion 1-8 assays: 99.97

LCAP; >99.99% e.e..

<sup>1</sup>H-NMR (400.25 MHz, D<sub>2</sub>O) δ 7.30 (m, 1H), 6.92-6.85 (om, 2H), 4.68 (OH), 3.75-3.66 (om, 3H), 3.45 (bm, 1H), 3.30-3.14 (om, 2H), 1.32 (s, 9H).

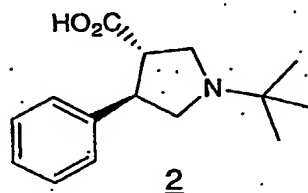
5 <sup>13</sup>C-NMR (100.65 MHz, D<sub>2</sub>O) δ 176.5, 162.8 (dd, *J* = 123.7, 12.6), 160.3 (dd, *J* = 124.5, 12.7), 129.9 (dd, *J* = 10.1, 5.9), 119.7, 111.7 (dd, *J* = 21.5, 3.6), 104.1 (t, *J* = 26.2), 62.0, 51.9, 51.0, 50.6, 41.3, 23.7 (3C).

MP (DSC): onset 215 °C, peak 217 °C :

Anal. Calcd for C<sub>15</sub>H<sub>19</sub>F<sub>2</sub>NO<sub>2</sub>: Calc., C, 63.59; H, 6.76; F, 13.41; N, 4.94. Found,

10 C, 63.50; H, 6.81; F, 13.11; N, 4.91.

## EXAMPLE 2



Compound 2 was prepared from 2-chloroacetophenone (Aldrich)

15 following a similar procedure to that described for compound 1-8.

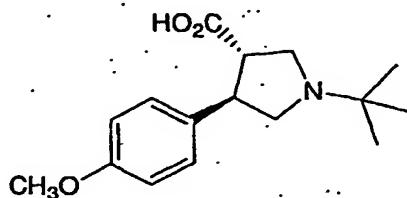
<sup>1</sup>H-NMR (400.25 MHz, CD<sub>3</sub>OD) δ 7.40 (m, 2H), 7.34 (m, 2H), 7.26 (m, 1H), 3.85 (m, 1H), 3.80-3.70 (m, 2H), 3.58 (br t, *J* = 10.5, 1H), 3.31 (m, 1H), 3.16 (dd, *J* = 18.8, 9.6, 1H), 1.43 (s, 9H).

<sup>13</sup>C-NMR (100.65 MHz, CD<sub>3</sub>OD) δ 175.5, 138.0, 128.4, 127.3, 127.2, 61.1, 53.7,

20 52.3, 51.9, 47.4, 23.5.

HR-MS M+H theoretical 248.1651; found 248.1649.

## EXAMPLE 3



Compound 3 was prepared from 4'-methoxy-2-bromoacetophenone (Aldrich) following a similar procedure to that described for compound 1-8.

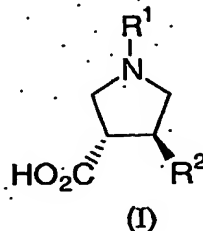
$^1\text{H-NMR}$  (400.25 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.31 (d,  $J = 8.7$ , 2H), 6.88 (d,  $J = 8.7$ , 2H), 4.89 (OH), 3.79-3.68 (om, 3H), 3.76 (s, 3H), 3.55 (br t,  $J = 10.6$ , 1H), 3.25 (br t,  $J = 11.2$ , 1H), 3.11 (dd,  $J = 18.8, 10.0$ , 1H), 1.41 (s, 9H).

$^{13}\text{C-NMR}$  (100.65 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  177.2, 160.7, 131.3, 129.9, 115.4, 62.6, 55.9, 55.2, 54.1, 53.3, 48.5, 25.0.

HR-MS  $\text{M}+\text{H}$  theoretical 278.1756; found 278.1754.

## WHAT IS CLAIMED IS:

1. A process for the preparation of compounds of structural formula (I):



wherein

R<sup>1</sup> is selected from the group consisting of

- (1) hydrogen,
- (2) amidino,
- (3) C<sub>1-4</sub> alkyliminoyl,
- (4) C<sub>1-10</sub> alkyl,
- (5) -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-7</sub> cycloalkyl,
- (6) -(CH<sub>2</sub>)<sub>n</sub>-phenyl,
- (7) -(CH<sub>2</sub>)<sub>n</sub>-naphthyl, and
- (8) -(CH<sub>2</sub>)<sub>n</sub>-heteroaryl,

in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R<sup>3</sup>; and alkyl, cycloalkyl, and (CH<sub>2</sub>)<sub>n</sub> are unsubstituted or substituted with one to three groups independently selected from R<sup>3</sup> and oxo;

R<sup>2</sup> is selected from the group consisting of

- (1) C<sub>1-4</sub> alkyl,
- (2) -(CH<sub>2</sub>)<sub>n</sub>-cycloalkyl,
- (3) -(CH<sub>2</sub>)<sub>n</sub>-heterocycloalkyl,
- (4) -(CH<sub>2</sub>)<sub>n</sub>-phenyl,
- (5) -(CH<sub>2</sub>)<sub>n</sub>-naphthyl, and
- (6) -(CH<sub>2</sub>)<sub>n</sub>-heteroaryl wherein heteroaryl is selected from the group consisting of

- (1) pyridinyl,
- (2) furyl,
- (3) thienyl,
- (4) pyrrolyl,
- 5 (5) oxazolyl,
- (6) thiazolyl,
- (7) imidazolyl,
- (8) pyrazolyl,
- (9) isoxazolyl,
- 10 (10) isothiazolyl,
- (11) pyrimidinyl,
- (12) pyrazinyl,
- (13) pyridazinyl,
- (14) quinolyl,
- 15 (15) isoquinolyl,
- (16) benzimidazolyl,
- (17) benzofuryl,
- (18) benzothieryl,
- (19) indolyl,
- 20 (20) benzthiazolyl, and
- (21) benzoxazolyl;

in which alkyl, phenyl, naphthyl, heteroaryl, and  $(CH_2)_n$  are unsubstituted or substituted with one to three groups independently selected from  $R^3$ ;

25 each  $R^3$  is independently selected from the group consisting of

- (1)  $C_{1-6}$  alkyl,
- (2)  $-(CH_2)_n$ -phenyl,
- (3)  $-(CH_2)_n$ -naphthyl,
- (4)  $-(CH_2)_n$ -heteroaryl,
- 30 (5)  $-(CH_2)_n$ -heterocycloalkyl,
- (6)  $-(CH_2)_n$  $C_{3-7}$  cycloalkyl,
- (7) halogen,
- (8)  $OR^4$ ,
- (9)  $-(CH_2)_nN(R^4)_2$ ,
- 35 (10)  $NO_2$ ,

- (11)  $-(CH_2)_nNR^4SO_2R^4$ ,  
 (12)  $-(CH_2)_nSO_2N(R^4)_2$ ,  
 (13)  $-(CH_2)_nS(O)_pR^4$ ,  
 (14)  $CF_3$ ,  
 5 (15)  $CH_2CF_3$ ,  
 (16)  $OCF_3$ , and  
 (17)  $OCH_2CF_3$ ;

in which heteroaryl is as defined above; alkyl, phenyl, naphthyl, heteroaryl,  
 cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three  
 10 substituents independently selected from halogen, hydroxy, oxo, C<sub>1-4</sub> alkyl,  
 trifluoromethyl, and C<sub>1-4</sub> alkoxy; and wherein any methylene (CH<sub>2</sub>) carbon atom in  
 R<sup>3</sup> is unsubstituted or substituted with one to two groups independently selected from  
 halogen, hydroxy, and C<sub>1-4</sub> alkyl; or two substituents when on the same methylene  
 (CH<sub>2</sub>) group are taken together with the carbon atom to which they are attached to  
 15 form a cyclopropyl group;

each R<sup>4</sup> is independently selected from the group consisting of

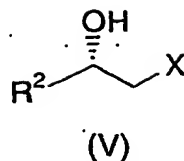
- (1) hydrogen,  
 (2) C<sub>1-6</sub> alkyl,  
 20 (3)  $-(CH_2)_n$ -phenyl,  
 (4)  $-(CH_2)_n$ -heteroaryl,  
 (5)  $-(CH_2)_n$ -naphthyl,  
 (6)  $-(CH_2)_n$ -heterocycloalkyl,  
 (7)  $-(CH_2)_nC_{3-7}$  cycloalkyl, and  
 25 (8)  $-(CH_2)_nC_{3-7}$  bicycloalkyl;

wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, and cycloalkyl are unsubstituted  
 or substituted with one to three groups independently selected from halogen, C<sub>1-4</sub>  
 alkyl, hydroxy, and C<sub>1-4</sub> alkoxy; or two R<sup>4</sup> groups together with the atom to which  
 they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally  
 30 containing an additional heteroatom selected from O, S, and NC<sub>1-4</sub> alkyl; and  
 n is 0, 1, 2, 3 or 4;

comprising the steps of:

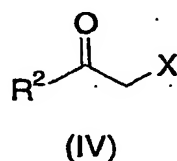
- (a) preparing an alcohol of structural formula (V)

2-36PV



wherein

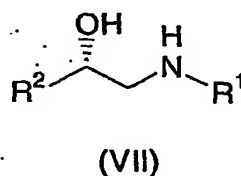
X is bromide or chloride, and R<sup>2</sup> is as defined above,  
by treating a ketone of structural formula (IV),



5

wherein X is bromide or chloride, and R<sup>2</sup> is as defined above, with a reducing agent,  
and isolating the resulting product;

(b) forming an amino alcohol of structural formula (VII)

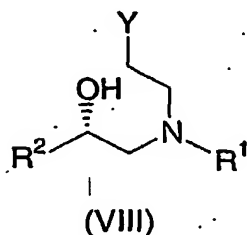


10

wherein R<sup>1</sup> and R<sup>2</sup> are as defined above,  
by treating the alcohol of structural formula (V) with an amine of general formula  
R<sup>1</sup>NH<sub>2</sub>, wherein R<sup>1</sup> is as defined above, and a base in a solvent, and isolating the  
resulting product;

15

(c) forming a compound of structural formula (VIII)



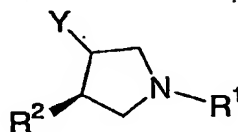
wherein Y is  $-\text{CN}$  or  $-\text{CO}_2\text{R}^5$  and  $\text{R}^5$  is  $\text{C}_{1-4}$  alkyl, and wherein  $\text{R}^1$  and  $\text{R}^2$  are as defined above,  
by treating the amino alcohol of structural formula (VII) with a compound of general formula (XI)



(XI),

wherein Y is  $-\text{CN}$  or  $-\text{CO}_2\text{R}^5$ , and  $\text{R}^5$  is  $\text{C}_{1-4}$  alkyl, and isolating the resulting product;

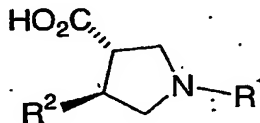
(d) forming a pyrrolidine compound of structural formula (X)



(X)

wherein Y,  $\text{R}^1$  and  $\text{R}^2$  are as defined above,  
by treating the compound of structural formula (VIII) with an alcohol activating reagent, followed by a base;

(e) forming a trans-pyrrolidine acid of structural formula (I)



(I)

wherein  $\text{R}^1$  and  $\text{R}^2$  are as defined above,  
by hydrolyzing the pyrrolidine compound of structural formula (X) with an aqueous base in a solvent; and



2408PV

(f) isolating the resulting product.

2. The process of Claim 1 wherein the reducing agent used to treat compound of formula (IV) of step (a) is (+)-DIP chloride.

3. The process of Claim 1 wherein the compound of formula (IV) of step (a) is treated with a reducing agent selected from the group consisting of borane-N,N-diethyl aniline, borane-THF, and borane-dimethylsulfide, in the presence of a catalyst.

4. The process of Claim 3 wherein the reducing agent is borane-N,N-diethyl aniline.

5. The process of Claim 4 wherein the catalyst selected from the group consisting of (S)-CBS and (S)-2-methyl CBS oxazaborolidine.

6. The process of Claim 5 wherein the catalyst is (S)-2-methyl CBS oxazaborolidine.

7. The process of Claim 1 wherein the alcohol of formula (V) is treated with an amine of general formula  $R^1NH_2$ , wherein  $R^1$  is selected from the group consisting of hydrogen,  $-(CH_2)_n$ phenyl, and  $C_{1-6}$ alkyl.

8. The process of Claim 7 wherein  $R^1$  is *tert*-butyl.

9. The process of Claim 1 wherein the alcohol of formula (V) is treated with a base selected from the group consisting of NaOH, LiOH, and KOH.

10. The process of Claim 9 wherein the base is NaOH.

11. The process of Claim 1 wherein, the compound of formula (XI) is the compound wherein Y is -CN.

12. The process of Claim 11 wherein the compound of formula (VIII) is formed by adding a 1:1 mixture of ethanol:formamide.

13. The process of Claim 1 wherein the amino alcohol of formula (VIII) is treated with an alcohol activating reagent selected from the group consisting of  $\text{ClPO}(\text{OR}^6)_2$ ,  $\text{ClPO}(\text{N}(\text{R}^6)_2)_2$ ,  $\text{MsCl}$ ,  $\text{Ms}_2\text{O}$ ,  $\text{TsCl}$ , and  $\text{Ts}_2\text{O}$ , wherein  $\text{R}^6$  is C<sub>1-4</sub> alkyl or phenyl.

14. The process of Claim 13 wherein the alcohol activating reagent is chlorodiethyl phosphate.

15. The process of Claim 1 wherein amino alcohol of formula (VIII) is treated with a base selected from the group consisting of lithium hexamethyl disilazide, sodium hexamethyl disilazide, and potassium hexamethyldisilazide.

16. The process of Claim 15 wherein the base is lithium hexamethyl disilazide.

17. The process of Claim 1 wherein the pyrrolidine compound of formula (X) is hydrolyzed with a base selected from the group consisting of  $\text{NaOH}$ ,  $\text{LiOH}$  and  $\text{KOH}$ .

18. The process of Claim 17 wherein the base is  $\text{NaOH}$ .

19. The process of Claim 1 wherein  $\text{R}^2$  is phenyl or thienyl optionally substituted with one to three groups independently selected from  $\text{R}^3$ .

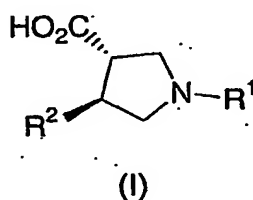
20. The process of Claim 19 wherein  $\text{R}^2$  is phenyl optionally substituted with one to three groups independently selected from  $\text{R}^3$ .

21. The process of Claim 20 wherein  $\text{R}^3$  is selected from the group consisting of halogen,  $-\text{CF}_3$ , and  $\text{OR}^4$ , wherein  $\text{R}^4$  is as defined in Claim 1.

22. The process of Claim 21 wherein  $\text{R}^2$  is selected from the group of phenyl; *ortho*, *para*-difluorophenyl; and *para*-methoxyphenyl.

23. The process of Claim 22 wherein R<sup>2</sup> is *ortho*, *para*-difluorophenyl.

24. The process of Claim 1 wherein the compound of structural formula (I) is isolated by forming a zwitterion of the trans pyrrolidine acid of structural formula (I)



wherein R<sup>1</sup> and R<sup>2</sup> are as defined above; recrystallizing the zwitterion from a solvent; and isolating the resulting product.

25. The process of Claim 24 wherein the zwitterion of the pyrrolidine acid of formula (I) is formed at the isoelectric pH using an acid.

26. The process of Claim 25 wherein the acid is selected from sulfuric acid or hydrochloric acid.

27. The process of Claim 26 wherein the acid is sulfuric acid.

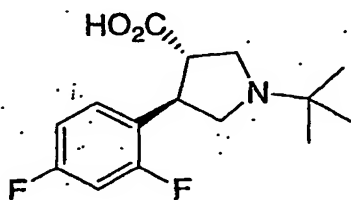
28. The process of Claim 24 wherein the zwitterion of the pyrrolidine acid of formula (I) is recrystallized from a solvent.

29. The process of Claim 28 wherein the solvent is selected from the group consisting of ethanol, isopropyl alcohol, methyl *tert*-butyl ether or a mixture thereof.

30. The process of Claim 29 wherein the solvent is a mixture of 1:3 isopropyl alcohol:methyl *tert*-butyl ether.

21588PV

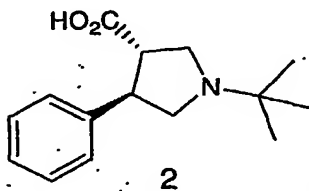
31. The compound 1-8



1-8 ;

or a zwitterion or salt thereof.

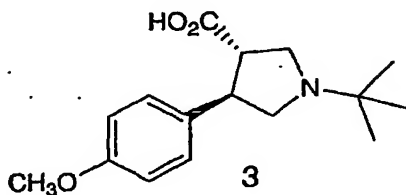
5 32. The compound 2



2 ;

or a zwitterion or salt thereof.

10 33. The compound 3

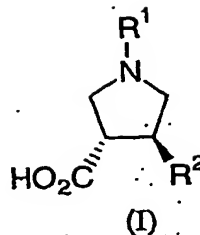


3 ;

or a zwitterion or salt thereof.

15 34. A process for the preparation of compounds of structural formula (I):

2138PV



wherein

R<sup>1</sup> is selected from the group consisting of

- 5 (1) hydrogen,
- (2) amidino,
- (3) C<sub>1-4</sub> alkyliminoyl,
- (4) C<sub>1-10</sub> alkyl,
- (5) -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-7</sub> cycloalkyl,
- 10 (6) -(CH<sub>2</sub>)<sub>n</sub>-phenyl,
- (7) -(CH<sub>2</sub>)<sub>n</sub>-naphthyl, and
- (8) -(CH<sub>2</sub>)<sub>n</sub>-heteroaryl,

15 in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R<sup>3</sup>; and alkyl, cycloalkyl, and (CH<sub>2</sub>)<sub>n</sub> are unsubstituted or substituted with one to three groups independently selected from R<sup>3</sup> and oxo;

R<sup>2</sup> is selected from the group consisting of

- 20 (1) C<sub>1-4</sub> alkyl,
- (2) -(CH<sub>2</sub>)<sub>n</sub>-cycloalkyl,
- (3) -(CH<sub>2</sub>)<sub>n</sub>-heterocycloalkyl,
- (4) -(CH<sub>2</sub>)<sub>n</sub>-phenyl,
- (5) -(CH<sub>2</sub>)<sub>n</sub>-naphthyl, and
- (6) -(CH<sub>2</sub>)<sub>n</sub>-heteroaryl wherein heteroaryl is selected from the group
- 25 consisting of
- (1) pyridinyl,
- (2) furyl,
- (3) thienyl,
- (4) pyrrolyl,

21583PV6

- 5
- (5) oxazolyl,  
 (6) thiazolyl,  
 (7) imidazolyl,  
 (8) pyrazolyl,  
 (9) isoxazolyl,  
 (10) isothiazolyl,  
 (11) pyrimidinyl,  
 (12) pyrazinyl,  
 (13) pyridazinyl,  
 10 (14) quinolyl,  
 (15) isoquinolyl,  
 (16) benzimidazolyl,  
 (17) benzofuryl,  
 (18) benzothienyl,  
 15 (19) indolyl,  
 (20) benzthiazolyl, and  
 (21) benzoxazolyl;

in which alkyl, phenyl, naphthyl, heteroaryl, and  $(CH_2)_n$  are unsubstituted or substituted with one to three groups independently selected from  $R^3$ ;

20

each  $R^3$  is independently selected from the group consisting of

- (1) C<sub>1-6</sub> alkyl,  
 (2)  $-(CH_2)_n$ -phenyl,  
 (3)  $-(CH_2)_n$ -naphthyl,  
 25 (4)  $-(CH_2)_n$ -heteroaryl,  
 (5)  $-(CH_2)_n$ -heterocycloalkyl,  
 (6)  $-(CH_2)_n$ C<sub>3-7</sub> cycloalkyl,  
 (7) halogen,  
 (8)  $OR^4$ ,  
 30 (9)  $-(CH_2)_nN(R^4)_2$ ,  
 (10)  $NO_2$ ,  
 (11)  $-(CH_2)_nNR^4SO_2R^4$ ,  
 (12)  $-(CH_2)_nSO_2N(R^4)_2$ ,  
 (13)  $-(CH_2)_nS(O)_pR^4$ ,  
 35 (14)  $CF_3$ ,

- (15)  $\text{CH}_2\text{CF}_3$ ,
- (16)  $\text{OCF}_3$ , and
- (17)  $\text{OCH}_2\text{CF}_3$ ;

in which heteroaryl is as defined above; alkyl, phenyl, naphthyl, heteroaryl,  
5 cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three  
substituents independently selected from halogen, hydroxy, oxo,  $\text{C}_{1-4}$  alkyl,  
trifluoromethyl, and  $\text{C}_{1-4}$  alkoxy; and wherein any methylene ( $\text{CH}_2$ ) carbon atom in  
 $\text{R}^3$  is unsubstituted or substituted with one to two groups independently selected from  
halogen, hydroxy, and  $\text{C}_{1-4}$  alkyl; or two substituents when on the same methylene  
10 ( $\text{CH}_2$ ) group are taken together with the carbon atom to which they are attached to  
form a cyclopropyl group;

each  $\text{R}^4$  is independently selected from the group consisting of

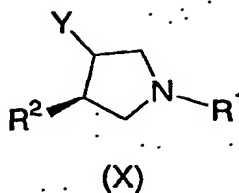
- (1) hydrogen,
- 15 (2)  $\text{C}_{1-6}$  alkyl,
- (3)  $-(\text{CH}_2)_n$ -phenyl,
- (4)  $-(\text{CH}_2)_n$ -heteroaryl,
- (5)  $-(\text{CH}_2)_n$ -naphthyl,
- (6)  $-(\text{CH}_2)_n$ -heterocycloalkyl,
- 20 (7)  $-(\text{CH}_2)_n\text{C}_{3-7}$  cycloalkyl, and
- (8)  $-(\text{CH}_2)_n\text{C}_{3-7}$  bicycloalkyl;

wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, and cycloalkyl are unsubstituted  
or substituted with one to three groups independently selected from halogen,  $\text{C}_{1-4}$   
alkyl, hydroxy, and  $\text{C}_{1-4}$  alkoxy; or two  $\text{R}^4$  groups together with the atom to which  
25 they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally  
containing an additional heteroatom selected from O, S, and  $\text{NC}_{1-4}$  alkyl; and  
 $n$  is 0, 1, 2, 3 or 4;

comprising the steps of:

- 30 (a) hydrolyzing a pyrrolidine compound of structural formula (X), wherein Y,  $\text{R}^1$   
and  $\text{R}^2$  are as defined above,

2138PV



with an aqueous base in a solvent; and

- 5 (b) isolating the resulting product.

35. The process of Claim 34 wherein the pyrrolidine compound of formula (X) is hydrolyzed with a base selected from the group consisting of NaOH, LiOH and KOH.

10

36. The process of Claim 35 wherein the base is aqueous NaOH.

37. The process of Claim 36 wherein R<sup>2</sup> is selected from the group of phenyl; *ortho*, *para*-difluorophenyl; and *para*-methoxyphenyl.

15

38. The process of Claim 37 wherein R<sup>2</sup> is *ortho*, *para*-difluorophenyl.



TITLE OF THE INVENTION  
PROCESS AND INTERMEDIATES FOR THE PREPARATION OF  
PYRROLIDINE CARBOXYLIC ACIDS

5 ABSTRACT OF THE DISCLOSURE

A novel process is provided for the preparation of pyrrolidine carboxylic acids, and the useful intermediates obtained therein. These compounds are intermediates for the synthesis of melanocortin-4 receptor (MC-4R), which are useful for the treatment of disorders such as obesity, diabetes, male sexual dysfunction, and  
10 female sexual dysfunction.